THE THYROID GLAND

BY

CHARLES H. MAYO

AND

HENRY S. PLUMMER

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PROFESSOR CHARLES H. MAYO

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The Committee wishes to credit, at the request of Doctor C. H. Mayo, the valuable assistance rendered by Doctor William A. Hendricks in the compilation of his paper.

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THE BEAUMONT FOUNDATION LECTURES

SUBJECT

THE THYROID GLAND

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PREFACE

The interest manifested in goiter problems is not only significant but of a sustained, abiding character, touching as it does wide and varied geographic areas and involving every phase of medical practice directly or indirectly. It is a subject holding and obscuring as yet its unknowns in such ways as to allure and fascinate the most ardent and best of clinical research workers.

The critical reader is ready to judge compilations and also reports from research workers with the same attitude of mind. The judgment is usually most severe when the authors write upon subjects of greatest familiarity to the reader. The responsibility then, should obviously, be keenly felt and seriously met by authors who offer further contributions to this widely studied subject.

The extent of work done upon thyroid disease can scarcely be comprehended, for internists, surgeons and laboratorians have been equally active in efforts to solve its riddles. The interpretation of results thus far attained is not easily made. It is most gratifying to the Beaumont Foundation Committee of the Wayne County Medical Society to present this opportunity to the readers of the Fourth Lecture Series of an authoritative résumé of thyroid disease from one of the greatest American medical centers and contributed by master students of the subject who have had unexcelled opportunities for investigations in all of its interesting phases. The Mayo Clinic has been favored in having the largest

group of thyroid cases ever assembled during a period of thirty-three years. This group, numbering 22,728 cases, required 30,628 operations.

The associated medical and surgical studies of such a large group of material carried on through so many years must appeal to all to vouchsafe the most authoritative pronouncement upon the subject ever given.

James E. Davis, A.M., M.D.
For the Committee.

THE THYROID GLAND

Charles H. Mayo, M.D.
Rochester, Minnesota

History of Goiter

The early story of goiter is voluminous, but very tangled. Traces of attempts to distinguish varieties are recorded among the writings of the ancients; later, however, and especially in the Middle Ages, scrofula and other diseases of the glands were confounded with it and treated as goiter. An unsightly and frequently fatal disease, goiter was accepted as an inoperable affliction in communities where it prevailed until late in the eighteenth century. Little progress was made until this time. The glands near the larynx, the "glandulae laryngae oppositae," as described at the commencement of this era do not differ from the descriptions furnished two centuries earlier by Vesalius.

According to Schreger, Celsus had already undertaken the extirpation of goiter but it is clear that in his use of this term in 45 A.D., he did not have the disease of the thyroid gland in mind but rather a swelling of the lymph-nodes. Of goiter proper he unmistakably speaks of the cystic type in an article entitled "De cervicis vitio," and says after the use of caustics, "sed scalpelli curatio brevior est." About the year 330 A.D. Albucasis undertook an operation for genuine goiter.

Down to the time of Paulus Aegineta (625-690 A.D.), the last great representative of ancient medical science, the Greek and Roman physicians used the name "bronchocele" for goiter, while the popular Latin names were "tumor gutturis," or "gutter tumidum." The chronic tumors of the lymphatic glands were designated

as "strumae," and the person afflicted with the condition was called "strumosus." From the "Juvenal" we learn that in Aegineta's time, goiter was so common that it had become proverbial and no longer excited surprise, but it does not seem that the severer forms of cretinism were known beyond the limits of the Alpine valleys.

Mandt, in *Rust's Magazine,* states that Amatus Lusitanus about the year 1550 related that an "audax homo" excised small goiters, and thereby exposed the trachea. One passage is entitled "De Strumis"; the other is entitled "De Strumis Dictis Scrofulosis." It is inferred that the author refers in the former to scrofulous abscesses and in the latter to swollen glands.

In 1550, Realdus Columbus, of Padua, the successor of Vesalius, threw more light on the subject. A few years afterward, Eustachio, professor of anatomy in Rome, discovered the isthmus of the human thyroid.

The first person to discover that goiter was a tumor of the thyroid was Fabricus of Aquapendente. Thomas Wharton was the first to write a monograph on this subject and to employ the term "thyreodea" in 1656.

In ancient times, goiter was treated either surgically or medically. The latter method consisted of the application of various plasters, usually containing resin or sea-salt, and the daily washing of the neck with seawater. Later the spongiae marinae ustae were favored remedies. At that time the hard, cancerous, and the vascular goiters were regarded as incurable.

During the latter part of the sixteenth century the historian Josias Simler gave an account of the cretins of the Valais. During the later half of the eighteenth century the famous naturalist, Horace de Saussure, called attention to cretinism during his travels in the Alps. It was he who noted the imperfect development of many of the inhabitants in the valleys which were

less than 3,000 feet above the sea level of the Mediterranean, attributing it to the heat and stagnation of the air which was shut in by lofty mountains.

In 1710, Forester, Fulvius Gherli, Petit, Roonhuysen, Hoin and Conrad Ludwig Walther were reported to have excised true goiters, but investigation of the literature reveals only two cases that could possibly be considered as goiter.

In 1752 appeared Fodere's classic work on goiter and cretinism. Fodere considered that cretinism was inherited from the father or mother, most commonly the former, and supposed that it had its origin in goiter. It is to be inferred from his writings that there were goitrous persons before there were cretins. His observations excited a general interest in the subject, and it was found that the disease prevailed in several other countries besides Switzerland. It occurred in the Harz Mountains and in the Carinthian and Styrian Alps. Fodere claims to have extirpated the thyroid, but only in cases of scirrhous degeneration. He also tells of a courageous surgeon, Giraudy, in Marseilles, who successfully removed two goiters.

In 1802, Joseph and Carl Wenzel of Vienna described cretinism as they found it in the mountainous parts of Salzburg, and gave as its cause the bad atmosphere in the deep valleys of this district.

The great physiologist, Haller, notes that calcareous and osseous substances had been met with in the dissections of enlarged thyroid glands. Fodere was unable to discover such depositions in any of the goiters which he dissected.

In 1842, Gerard Marchant presented a thesis to the Faculty of Medicine in Paris on cretinism as it appeared in the Pyrenees. He remarked that moisture of the soil and dampness of the atmosphere greatly influenced the production of cretinism and goiter.

Bruberger gives an account of the surgical treatment of goiter from 1785 to 1876. The important work of Gunther he undoubtedly overlooked as no mention was made of it. Gunther carried the story of the operation up to 1861 and collected records of forty-one cases but overlooked sixty-five others, of which seventeen were reported in France, thirteen in Italy, twelve in Great Britain, eight in the United States, and twenty-five in Germany. Briére's collation from Schmidt's *Jahrbücher* gives the history of the operation from 1845 to 1876. The study is original and possibly furnished Suskind material for his monograph of that time.

Suskind continued the operative story introduced so comprehensively by the scholarly Gunther and carried by him from the beginning of the Christian era to the middle of the nineteenth century. Suskind writes that at the end of the eighteenth century when the first triumphs of the operation were being celebrated in Germany it was emphatically condemned in France by all of the members of the influential Academy of Surgeons of Paris except Desault, who was the first French surgeon to whom the excision of a struma was accredited. It was also condemned in Germany by most surgeons, even three-fourths of a century later. In certain countries until after 1890 attempts were made to reduce the size of a goiter by the use of setaceum, wick, hair seton, cannula, incision and drainage; by the injection of iodin, tincture of chlorid of iron, turpentine, and so forth, by caustics and by the actual cautery; by subcutaneous and indeed, extracutaneous ligature; by debridement and by morcellement.

In 1883 the operation performed by Desault in 1791 had not been improved on in France. England made no operative contributions of importance, but Scotland could congratulate herself on the work of Patrick Heron Watson (1874) who was the only surgeon except Bottini

of the four great nations, France, Italy, Great Britain and America, to perform more than four lobectomies and to devise a method regarded at the time as worthy of adoption.

Luigi Porta in his great classic *Delle alterazioni patologiche delle arterie per la legatura e la torsione,* published in Milano in 1845, may have premised that of the various procedures which might be employed to reduce the size of a goiter, he would first test the effect of ligation of the thyroid arteries. After ligating one superior thyroid artery in two cases without benefit, he ligated, simultaneously, both of the superior arteries in his third case and noted an appreciable reduction in the size of the goiter, from which he concluded that the inferior thyroid artery should also be tied. To Luigi Porta is credited the first definition and recommendation of the operation of enucleation and resection for adenoma.

In the United States and Canada forty-five operations for goiter were recorded up to 1883. Five deaths resulted, one from pneumonia. Even including this case the mortality was only 11 per cent, excluding it, 9 per cent. In these early cases the names of Nathan R. Smith, E. S. Cooper, Warren W. Greene, E. L. Marshall, F. F. Maury and C. E. Fenwick deserve mention.

Kocher, only a few months after Gull, observed a peculiar idiopathic condition in adults to which two years later Ord gave the name myxedema, many years prior to Murray's discovery in 1892 that operative myxedema could be dissipated by the administration, subcutaneously, of thyroid extract.

Sick, in 1867, was perhaps the first to perform successfully what was, except for a possible remnant on the trachea, a total lobectomy.

Greater advance was made in the operative treatment of goiter in the decade from 1873 to 1883 than in all

previous years. Unquestionably this rapid progress was due chiefly to the possibilities and the impetus given by the introduction of antiseptic surgery.

In 1883 Kocher published a paper in which he standardized the operation of lobectomy. In the ten years preceding the publication of this paper he had performed 101 operations on the thyroid gland, and in the last seventeen months he had operated on thirty-nine patients with nonmalignant goiter with but two deaths. No deaths occurred from sepsis or hemorrhage. He was able to gather reports of 240 cases of nonmalignant goiter operated on since 1877; in this series there was a mortality of only 11.6 per cent. During the same period (1877 to 1883) he collected reports of twenty-eight cases of malignant struma with sixteen deaths. Of 600 new surgical cases of Kocher described in 1898, 556 were colloid strumas. For more than two years he had employed cocain anesthesia. Chloroform was the cause of the only fatality in this series. At the time of his death in 1917 approximately 5,000 cases of goiter had been operated on at his clinic.

In 1917 the practical application of a method to prevent simple goiter was started in the public schools of Akron, Ohio, by Marine and Kimball. Their plan was to saturate the thyroid with iodin each year, and 2 gm. of sodium iodid were given over a period of two weeks each spring and fall.

In the United States, Crile, Ochsner, Halsted, and C. H. Mayo have done the most important work in the field of goiter surgery.

At the Mayo Clinic from 1912 to 1922 inclusive there were 20,961 resections of the thyroid, with five deaths from pulmonary embolism, or one in 4,484 cases. During the same period there were 6,493 ligations of thyroid arteries, with one death from pulmonary embolism.

During the year 1922, 1,983 operations were per-

formed on the thyroid gland, with but nineteen surgical deaths, a mortality rate of 0.96 per cent. This number includes 663 thyroidectomies on 663 patients with adenomatous goiter without hyperthyroidism, with but one death, a mortality rate by case of 0.15 per cent. The highest death rate was in cases of adenomatous goiter with hyperthyroidism, there being seven deaths following 201 thyroidectomies on an equal number of patients, or a mortality rate, by case, of 3.48 per cent. In these cases the myocardial degeneration is greater, and as much as, or more than, the average in exophthalmic goiter. There were 1,093 operations in 1922 for exophthalmic goiter, with a mortality rate, by operation of 1 per cent. The operative mortality by case, however, is the significant figure in exophthalmic goiter, and in our series for 1922 was less than 2 per cent (1.99), and the mortality rate for thyroidectomy in exophthalmic goiter was less than 1 per cent (0.96).

In 1924 at the Mayo Clinic, the total number of surgical goiter cases, both exophthalmic and simple, was 1,785, with a mortality of ten (0.58 per cent). The total number of goiter operations, both exophthalmic and simple, was 1,928, with a mortality of ten (0.51 per cent).

Cases from 1892 to 1925 (inclusive)	22,728
Operations from 1892 to 1925	30,628
Cases of exophthalmic goiter	8,223
Cases of adenomatous goiter (including those with hyperthyroidism)	14,505
Operations for exophthalmic goiter	15,737
Operations for adenomatous goiter (including those with hyperthyroidism)	14,891

In the earlier days of thyroid surgery the relatively high mortality rate influenced the decision of many patients with exophthalmic goiter to seek means of cure

other than surgery. Many of these finally came to operation late in the course of the disease, when the operative risk was increased and when the prospect of complete cure was greatly diminished. The knowledge of the benefits derived from surgery has gradually become disseminated, and today a much larger proportion of patients with exophthalmic goiter seek surgery primarily, early in the course of the disease, when the risk is less and the prospect of complete cure is greatest.

Anatomy of the Thyroid Gland

The thyroid gland lies on the lateral surface of the thyroid and cricoid cartilages and on the anterolateral surface of the upper end of the trachea, which it surrounds in a more or less horseshoe manner.

It consists of two lobes united by a narrow transverse portion, the isthmus. The lobes are conical in shape, about 5 cm. long, 3.13 cm. wide and 1.88 cm. thick.

Internally each lobe comes in contact with the trachea, esophagus, thyroid, and cricoid cartilages, the inferior laryngeal nerve, the inferior constrictor of the pharynx and the posterior portion of the cricothyroid muscle. Its posterior surface is in relation with the carotid sheath containing the common carotid, the internal jugular vein and the vagus nerve. It is, furthermore, in relation with the inferior thyroid artery, the parathyroids and also the prevertebral fascia and muscles. The anterolateral surface is covered by the sternothyroid, the sternohyoid and the omohyoid muscles. The sternocleidomastoid muscles overlap the outer border of the gland.

From the isthmus or from the adjacent part of either lobe, there is, in many cases, a narrow strip of glandular tissue which passes in front of the thyroid cartilage upward toward the hyoid bone to which it may or may not be attached. This is called the pyramidal process;

in rare cases it may be double. This process represents the vestiges of the thyroglossus duct.

Accessory thyroids frequently occur in the neck; they are most common in the neighborhood of the hyoid bone, but they may be found below the thyroid gland as far down as the arch of the aorta and the bifurcation of the trachea. They have the same histologic structure as the thyroid gland itself.

The thyroid gland receives its blood supply from two arteries, the superior and the inferior, and sometimes a third, the "ima." The superior thyroid artery is the first branch of the external carotid. The inferior thyroid artery arises from the thyrocervical trunk given off by the subclavian artery. The "ima" artery when it exists, comes off directly from the arch of the aorta or from the innominate artery and terminates in the isthmus.

It has been demonstrated that each artery supplies a certain region. The superior artery supplies the superior half of the lobe, the inferior thyroid artery the inferior half. This is very schematic and is not literally true, as both arteries anastomose freely, and in time may grow into an important collateral circulation. If all the arteries are injected, not only the whole thyroid gland, but the adjoining organs will become injected at the same time.

The veins of the thyroid gland show considerable variation; they form a rich plexus on, and beneath, the capsule of the gland. The superior thyroid vein terminates generally in the thyro-linguo-facial trunk; this trunk empties into the internal jugular vein. Not infrequently a middle vein emerges from the side of the gland, passes transversely outward and empties into the internal jugular vein. From the lower border of the isthmus and both poles there is a plexus of two, three, or more veins which go directly downward and empty

into the innominate vein on both sides. These are known as the imae veins.

The blood supply of the thyroid gland is very extensive, and in proportion to its size the circulation here is more extensive than in the brain. The thyroid in proportion to its weight, which varies from 1 ounce to 1.5 ounces, has three and four-tenths times the circulation of the brain, and about five and one-half times the circulation of the kidney. The abundance of the circulation shows that the function of the thyroid gland must be an important one and the secretion must be rapidly oxidized.

The nerve supply comes from the sympathetic and from the vagus nerves, the median and inferior cervical ganglia from the former and the superior laryngeal branch from the latter. The inferior laryngeal nerve comes in close contact with the gland but does not supply it.

Physiology of the Thyroid Gland

The importance of the thyroid gland in the adequate discharge of the functions of the organism was brought out in 1883 by Reverdin and Kocher. These observers were impressed by the disastrous results of total thyroidectomy which was then practiced as the operation of choice. At first Kocher attributed the symptoms to atrophy of the trachea and to a defect in respiration which resulted in severe anemia and this in turn in cachexia, while Reverdin thought that they were due to an intrathyroid vasomotor center. Schiff and Wagner, and subsequently P. von Bruns and Grundler (1884) appear to have been the first to attribute the symptoms which followed total removal of the gland to the loss of its functions. The condition was termed operative myxedema.

For quite a long time the thyroid was considered as a mechanical regulatory organ of the circulation of the blood and was regarded as an arterial reservoir intercalated between the cephalic and the carotid-subclavian systems; when filled with blood, the gland was thought capable of compressing the carotids, thus diminishing the quantity of blood going into the brain. The thyroid was then regarded as a safety vent for the cerebral circulation.

One of the most curious theories of the physiology of the thyroid was that of Fomeris. According to this author the organ played an important part in the physiology of sleep; it swelled up during sleep because it retained a certain portion of the blood, destined for the brain, which this gland gave off during the daytime.

In 1840 Astley Cooper noticed that thyroidectomy in animals was followed by a peculiar symptom-complex, but he did not test his observations experimentally.

We propose to speak of the thyroid secretion as if it were one consistent entity, although this is not scientifically accurate. Its first function is morphogenetic, which duty it shares with the pituitary, the thymus, the suprarenal cortex and the testicle. This action is not exerted to the same extent on all tissues or on all organs. This morphogenetic action also has an effect on the development of the nervous system. Thyroid inadequacy interferes with the proper development of the nervous system much more than inadequacy of any of the other glands mentioned.

A further function of the thyroid gland is to regulate the normal processes of the various physiologic mechanisms. This action is exerted by a stimulating substance, which, according to Gley, is the only one entitled to the designation of hormone, it being the most powerful excitant of nitrogenous and respiratory exchanges. This

action is essentially catabolic, and is therefore, antagonistic to the morphogenetic action, which is essentially anabolic.

The third function of the thyroid is to neutralize certain toxic products of normal metabolism. Moebius considered that this action was exerted by the secretion of the gland. This explanation of neutralization has, however, been discarded recently in favor of the belief that it is due to its stimulant action. If such a function really exists, the blood of an athyroidic subject should be loaded with injurious substances which have not been neutralized (Hara and Branovacki). Experiments have been performed which suggest that this is really the case. It seems probable that both processes, stimulation and neutralization, go on together and that the dwarfism of the athyroidic subject is the result of a simultaneous failure of stimulation and an excess of inhibition.

The fourth function of the thyroid is that of defense against bacterial invasion. This view is very theoretical, but of course the thyroid plays an indirect part in the struggle against infection because its secretion participates in most of the vital functions.

The classification of diseases of the thyroid employed by Plummer is the simplest possible: (1) colloid or simple goiter, (2) adenoma without hyperthyroidism, (3) adenoma with hyperthyroidism, (4) exophthalmic goiter, (5) cretinism, (6) myxedema, (7) thyroiditis, (8) malignancy, and (9) anomalies.

The first four of these groups more often concern the surgeon, as they represent the enlargement of the thyroid gland. The surgeon is responsible for certain of the increasing number of cases of myxedema which have resulted from operation on simple colloid goiters, or from too extensive removal of the gland.

Colloid goiter usually responds to treatment by iodin

or thyroid preparations, and only occasionally is considered a surgical disease.

Adenomatous goiter without hyperthyroidism should be treated by removal of the adenomatous masses with as little destruction of gland tissue as possible, and the remaining colloid reduced by medication.

Adenomatous goiter with hyperthyroidism is primarily surgical. Patients with adenomatous goiters of long standing often develop symptoms of hyperthyroidism which quite closely resemble those of exophthalmic goiter. This group represents those cases usually designated as pseudo-Graves' disease, or formes frustes, long considered an irregular or incomplete form of exophthalmic goiter. Plummer, however, has presented sufficient evidence to prove that this disease is separate and distinct from that of exophthalmic goiter.

Exophthalmic goiter has been subject to a great deal of controversy medically. The goiter, if not operated on, causes ill health over a long period, and of itself has a considerable mortality, although a number of patients with mild forms recover spontaneously. Successful reduction of the gland tissue by surgery is followed by a most spectacular and immediate disappearance of symptoms in the greater number of cases. The progress of medical knowledge concerning exophthalmic goiter has been greatly delayed by reason of the influence of certain clinicians, who, recognizing the associated involvement of the central nervous system, felt that it was a disease of that system rather than a local condition, due to an abnormal secretion of the thyroid, and having a secondary effect on the central nervous system. Plummer's observation shows that the secretion of the thyroid gland acts similarly to a catalytic agent, accelerating the rate of formation in the cell of a quantum of potential energy. The metabolism is increased in hyperthyroid states because of an increase

in the amount of the catalyst available, and inversely is decreased in myxedema because of a decrease in the amount of the catalytic agent. Plummer, by metabolic methods which have been confirmed by Boothby, demonstrates that under normal conditions the amount of active thyroxin in the body is approximately 14 mg. Kendall has succeeded in separating and analyzing the active principle of the secretion of the thyroid gland, which he designates "thyroxin." He also has determined the empirical and structural formulas of thyroxin. Various compounds closely related to thyroxin have been formed synthetically, but not yet studied physiologically. As pointed out by Plummer, it is not unlikely that in exophthalmic goiter the characteristic symptoms peculiar to that disease, which are absent in adenomatous goiter with hyperthyroidism, are due to an imperfect form of the thyroxin molecule; his investigations suggest that in some way this variation may be due to an insufficient number of iodin atoms on the thyroxin nucleus. Kendall has further pointed out that the chemical properties of thyroxin and its probable antecedents are in accord with the theories of Plummer, based on clinical physiologic studies. It is possible that in exophthalmic goiter, characterized pathologically by diffuse parenchymatous hypertrophy, the gland is driven so hard by some unknown stimulus that the resulting secretion is more toxic than the normal secretion, or by its peculiar affinity for certain tissues produces the characteristic symptoms that differentiate the typical case of exophthalmic goiter from adenomatous goiter with hyperthyroidism. In short, adenomatous goiter with hyperthyroidism is pure hyperthyroidism, and exophthalmic goiter is hyperthyroidism plus disthyroidism. Probably the greatest contribution to the safety of operation in exophthalmic goiter was made by Plummer in showing that the opinion commonly held formerly, that iodin

should not be given to patients with true exophthalmic goiter, is incorrect. He shows that, when iodin is given in excess, those symptoms peculiar to, and characteristic of, exophthalmic goiter as contrasted with those of adenomatous goiter with hyperthyroidism largely disappear. This procedure, if appreciated by the surgeon, will immediately reduce his mortality rate by improving the resistance of those patients whose condition was formerly considered so dangerous. Cases of true exophthalmic goiter and of the hyperthyroidism of adenoma are to be recognized by increased metabolism, and thus operation is avoided on patients with no increased metabolic rate, who have other forms of nervous trouble, such as dementia praecox, psychoneurosis and cardiac neurosis. The loss of much thyroid through unnecessary operation will in the end be harmful to such patients, even though the immediate mental condition may be somewhat improved as a result of the psychic stimulus derived from a surgical procedure reinforced by the enthusiasm of a brilliant surgeon.

Etiology of Goiter and Development of the Thyroid

Various theories are held as a basis for the cause of goiter; the first and frequently mentioned is the one which ascribes the origin of goiter to inorganic or organic chemical substances contained in the water, derived from the soil through which the water percolates. This is a very old view, and has been advocated particularly by Bircher and Kocher. Another theory is the toxic infective theory; this assumes the existence of a specific infective agent (Kutschera) or, at any rate, specific intestinal flora, the toxic products of which affect the thyroid gland (Gaylord, McCarrison, Galli-Valerio, Messerli).

The organisms whose toxins exert the most marked

influence on the thyro-parathyroid glands are those whose normal habitat is the alimentary tract: *Bacillus coli* and its variants, certain unclassified "anaërobes," "dysenterio bacilli" of all classes, "cholera," and according to Farrant, the *Bacillus diphtheriæ*. Toxins absorbed into the system in cases of extensive burns also exercise a pronounced destructive action on the secreting cells of the gland. It is thought that the migration into the blood stream and organs of bacteria or other organisms from the alimentary canal and the action of these on the thyroid gland may have some influence on the intestinal intoxication. It is not surprising, therefore, to find that Rosenow has grown streptobacillus of definite characteristics from a number of thyroids removed at operation in cases of Graves' disease.

A third theory of the causation of goiter is that of lack of iodin in the food, which was formulated by Prevost in 1849 and by Chat in 1851.

Still another theory is that of multiple causation in relation to general hygiene. During the last century this theory has obtained adherents among such great authorities on goiter as Lebert, Demme, Troxler and Grassi.

Among the diseases having a deleterious action on the thyroid are: measles, mumps, whooping cough, scarlatina, bronchopneumonia, acute miliary tuberculosis, diphtheria, secondary syphilis, acute tonsillitis, acute rheumatic fever, malaria, trypanosomiasis, helminthiasis, rheumatoid arthritis, pyorrhea alveolaris, and most intestinal disorders. It is thought that these diseases especially the infectious diseases of childhood, may give rise to chronic inflammatory processes which manifest themselves by producing thyroid insufficiency after the disease has been cured. Chronic debilitating diseases exert a harmful influence on the thyroid, partly owing

to their impairment of nutrition and partly to the toxic action of the products of their causal agents, which result in a depreciation of the thyroid's reserve store of energy. Various other factors, such as altitude, season, sex, dentition, puberty, menstruation, marriage, pregnancy, and diet, may increase the activity of the thyroid apparatus. All of these factors come within the limits of the gland's normal physiologic range of action. It is thought probable that the slight fullness of the neck, to which they occasionally give rise, is due normally, to the increased flow of blood to the gland occasioned by its increased physiologic action. When, however, there is even slight toxic provocation, and especially when several of these influences are combined in the same individual, or there is a congenital impairment of the function of the gland, the limits of its normal functional range of action may be overstepped, and hyperplasia and hypertrophy, or in debilitated persons, atrophy may result. These provocations of abnormal action may be classified as nutritional, infectious, and psychic, and may be due to defective or improper food supply, insanitary surroundings, bacterial or other toxins, infectious diseases, intestinal stasis and constipation, fright, grief, worry, and mental distress and heredity. Congenital goiter is the most common hereditary manifestation of the cretinic degeneration although it is much less common than the acquired. Its incidence varies in different districts. In severely affected Himalayan villages as high as 60 per cent of breast-fed children show congenital goiter. On the other hand, cretinism in the offspring is usually preceded by goiter in the parent. Ninety-six per cent of the mothers and 40 per cent of the fathers of cretins had goiter. The development of congenital goiter would seem to be compensatory as well as possibly due to a hereditary defect in the thyroid apparatus of the child.

Development of the Thyroid

During fetal life the developing thyroid is peculiarly susceptible to influences which impair the mother's thyroidal resources. It responds to these influences by undergoing hypertrophy or hyperplasia, or cell-death or fibrosis. It is, therefore, important to exclude all influences which depress or unduly strain the maternal thyroid. For this reason it is sometimes wise to inquire into the antenatal history of backward children and to examine the mothers for thyroid defect.

The thyroid apparatus of the fetus and of young infants contains little or no iodin. At this period of life the thyroid is more cellular and the vesicles smaller and fewer, containing less colloid than in later years. Apparently nature does not intend the organ to attain full functional perfection until some months after birth nor is this gland called on to exercise its full powers during the earlier months of life. This is due to the fact that the maternal thyroid continues in a state of heightened activity throughout the earlier months of lactation, during which time the infant derives from its mother's milk, part, at least, of the thyroid secretion which it needs. Cow's milk does not provide this thyroidal element in the same degree or kind. Therefore, no form of infant feeding can replace the mother's milk.

With the cessation of suckling and with the commencement of taking more solid food, the thyroid apparatus of the child begins to act for itself, elaborating its secretion from the raw materials of the food and responding to every call made on it by the processes of increasing growth and the maturation of the bodily functions.

Throughout child life the thyroid is in a state of constant activity which may manifest itself, especially under

slight toxic provocation, in hypertrophy of the organ at about the period of the second dentition. At puberty, also, and with the onset of menstruation, the physiologic capacity if the organ is strained to the utmost, and hypertrophy is likely to occur. The parathyroids also share in this increased physiologic action. During menstruation the special function of the apparatus in maintaining the plasticity of the blood and governing calcium metabolism is called on, since there is a great loss of calcium with the menstrual flow. The efficient development of the sex organs and the stimulus to mental and physical growth which they in turn provide, are dependent on the functional perfection of the thyroid.

In women there can be no doubt of the benefits which marriage and childbearing confer, which are due, among other causes, to the maintenance of healthy thyroidal activity.

Increasing years bring to the thyroid the changes incident to advancing life, and after the age of forty its arteries become thickened and less elastic. Small cysts may arise in consequence, or calcareous deposits occur in its substance. Its epithelium becomes less active, its colloid, and with it its iodin content, decreased; in other words, the gland undergoes a process of slow atrophy.

The thyroids of a high proportion of healthy animals living at sea level, or at altitudes 1,000 feet above it, are in the colloidal or resting state, but functional activity appears to increase with residence at greater altitudes. This increased action is necessitated by the gland's influence in maintaining the red cells and hemoglobin at a level appropriate to the altitude, an increase in altitude calling for a rapid rise in the red cell and hemoglobin content of the blood.

Ordtmann found the thyroid gland to consist of 81.24 per cent of water, 17.66 per cent of organic matter, and 0.1 per cent of inorganic matter, of which iodin is the greatest constituent.

After iodin was discovered by Courtois in 1812, Straub, of Berne, suggested that it was the active principle of the "toasted sponges" and "aethiops vegetalis," both of which had been used for centuries in the treatment of goiter. Ever since its discovery iodin has been universally employed for diseases of the thyroid. In 1895, Kocher suggested examining thyroids for that element. The same year Baumann discovered an element in the thyroid which he called "iodothyrin." This he considered the active principle of the gland. Oswald isolated from the thyroid two different substances: the thyreoglobulin and the nucleoproteid. The first one he stated may or may not contain iodin; when it contains iodin, it is called iodothyreoglobulin. The nucleoproteid is free from iodin but contains great quantities of phosphorus. Both substances enter into the composition of colloid.

Iodin was found in the glands of newborn babes whose mothers had been fed with iodin, but none in the glands of babes whose mothers had not been fed with iodin during pregnancy. Marine and Lenhart have recorded similar results in animals. The quantity of iodin in a gland is dependent on the quantity of colloid and on the quantity of thyreoglobulin in the colloid.

Iodin is found not only in the thyroid gland, but also in a great many other organs, such as the muscles, suprarenal bodies, hypophysis, liver, kidneys, central nervous system, thymus, spleen and lymph-nodes. In the parathyroids, according to Gley and Lafayette, the quantity of iodin is even larger than in the thyroid.

The iodin content of the thyroid increases if the food

contains iodin. The foods which contain the most iodin are: asparagus, carrots, beans, mushrooms and fish. Hayhurst says that of the dependable sources of iodin in nature, sea air, sea food and sea water, it is to sea food that inland dwellers should look.

Smith and Broders found that external applications of tincture of iodin increased to a considerable extent the iodin content of the gland, also that potassium iodid given internally or hypodermically increased the iodin content of the gland very materially. Iodin in sea water, as stated by Hayhurst, exists to the extent of 0.01 gm. for each liter, and quoting Gautier, occurs in three forms: for the most part in organic combinations dissolved in the sea water, a small portion also in the organic form in sea organisms, and a further small portion in the inorganic form, but occurring only at great depths.

Thyroxin

Kendall, in 1914, was the first to isolate from the thyroid a crystalline substance (iodin, 60 per cent), the definite chemical formula of which was determined in 1917. It is locked in a protein molecule and can be obtained only by reaction of carbon dioxid on the thyroid. This substance has been called "thyroxin," and has been shown to be trihydro-4, 5, 6, tri-iodo-2 oxybeta-indolpropionic acid. Its chemical formula is $C_{11}H_{10}O_3NI_3$ ($C_{11}H_{10}O_3NI_3$). It possesses the same physiologic action as the gland itself. It was synthesized in 1919. According to Kendall, the thyroxin content in the tissues of the normal person is as constant as the number of red blood cells. The total amount of thyroxin in the tissues of the body is about 13 mg. By alkaline alcoholic hydrolysis Kendall separated the thyroid proteins into two groups: Group A, soluble in acids; and Group B, insoluble in acids. By continued

hydrolysis the Group A compounds and in final analysis the crystalline iodin-containing thyroxin proteins were further separated; no definite crystalline compound was obtainable from Group B. The latter group does not contain thyroxin.

Physiologically speaking, Group B does not produce any toxic effects, while Group A produces all the symptoms observed in hyperfunction of the thyroid. The severity of these symptoms is in direct proportion to the amount of iodin contained in the intermediary compounds up to the crystalline form. The amount of A-iodin compound necessary to produce symptoms is extremely small. One-half milligram daily produced marked symptoms in a cretin. Cardiac nervous hyperactivity, as well as increased general metabolism, is observed. When administered to hypothyroid patients, thyroxin exerts as favorable an influence as thyroid extract itself. Normal animals treated with this compound show the striking effects of metabolic stimulation parallel to the effects of thyroid intoxication.

Thyroxin is a white crystalline substance with the properties of a very weak acid. It is extremely insoluble in water (1:1,000,000), but is readily soluble in sodium hydroxid. The most striking characteristic of thyroxin is its iodin content. It contains 65 per cent of iodin, which is very firmly attached to the organic nucleus and is not easily broken off with sodium hydroxid, although it is very easily broken off by the action of sunlight.

Bacteriology of Goiter

Rosenow has isolated an anaërobic gram-positive diplobacillus-like organism from the excised thyroid gland in twenty-five of thirty-two cases of goiter (mostly

exophthalmic) in man, from the blood on two occasions in a severe case of exophthalmic goiter, and in conjunction with Dr. Mann, in eight of twelve dogs with goiter. They failed to obtain this organism from the gland in six of seven dogs showing apparently normal-sized thyroid glands, while the other showed a few colonies.

Rosenow injected a series of animals with fresh cultures of the diphtheroid streptococcus. Of the sixty-eight animals injected with strains from sixteen patients (ten with exophthalmic goiter and six with nontoxic goiter), and examined soon after injection, thirty-four (50 per cent) developed gross lesions in the thyroid. The incidence of lesions in other organs was about the same as in other similar experiments. Marked dilatation of blood vessels and hemorrhage in the interstitial tissues or acini were found microscopically in ten of fourteen dogs, eleven of thirteen rabbits, and five of eight guinea pigs injected from one day to four days previous to necropsy. Bacteria were in most cases not demonstrable microscopically in sections of the thyroid tissue. In a series of sixteen dogs that were injected repeatedly and allowed to live for from twenty to seventy days after the first injection, loss in weight and enlargement of the thyroid gland occurred, and diarrhea developed. One also developed softening, pulsation, and bruit of one lobe of the thyroid, associated with marked tachycardia and tremor.

A watery appearance on cross section of the thyroids was usual in the animals that developed symptoms. Microscopically, there were found vacuolization and irregular staining of the colloid, colloid within vessels, areas of necrosis, and a variable degree of hyperplasia, in certain instances extremely marked. Microörganisms were either few or not demonstrable.

Geographic Distribution and Incidence According to Race, Sex, and Age

Endemic goiter is distributed over the whole world. Few countries appear to be entirely free from it. It is so common in certain parts of England and Scotland as to be distinguished by the names, "Derbyshire neck" and "Nithsdale neck." It is most prevalent in temperate and subtropical zones, although it also occurs in regions of great cold, as in parts of Siberia, in Finland, and in the Hudson Bay territory; and in regions of great heat, as in tropical South America, Borneo, Sumatra, Java, India and Ceylon.

The chief points of endemic cretinism in Europe are the Central Alps, from which areas of this type radiate in various directions. Thus the disease is common in Switzerland, the Tyrol, Carinthis, Steiermark, the Savoy, Basses Alpes, Alpes-Maritimes, and Haute Garonne. There are also a number of secondary centers in mountainous districts or deep valleys, such as the Carpathians, the Vosges, Cevennes, the German mountains, the Pyrenees, the English Pennine, Cotswold and Mendip ranges, although the disease is rare in the Scottish Highlands and the Norwegian mountains. This tendency of the disease to appear in mountainous districts is not limited to Europe, for marked endemic areas are found in the Caucasus mountains, the Ural and Altae ranges, the Himalayas, the Abyssinian mountains, the Andes, the Cordilleras, and the mountains of Japan and the Asiatic islands.

Cretinism is, however, by no means confined to the mountainous areas, for the disease flourishes in the plains of Lombardy, Piedmont, Venice, and Alsace and also in river and lake basins, and deltas, as, for examples, the Struma River in the Balkans, so named from the prevalence of goiter on its banks (Crotti), the Lena and Obi in Russia, the Ganges, Indus, Brahmaputra

and other Indian rivers, the Great Lakes, and the St. Lawrence River in America. Crotti mentions a river in Brazil called the Quay-qui-raro or "Thick neck maker" on account of its goitrigenous qualities.

Several writers call attention to the prevalence of the disease in marshy regions and inundated areas, along canals. If one bank of a river is a marshy region, and the other high land, the former will be affected (for example, the Ganges). The islands of Madagascar, Ceylon, Borneo, Sumatra and Java have endemic foci, and even those such as the Azores, which are distant from other lands.

The seacoasts, although formerly claimed to be entirely free from goiter and cretinism, are occasionally affected. McCarrison mentions the following endemic (littoral) regions: the Ganges delta, the Island of Cutch in Manila Bay, the Island of Arran off the coast of Algeria, Glamorganshire, and certain shores of the Mediterranean, such as Istria and Dalmatia.

Race.—All races, Caucasian, Mongolian, Malayan, and Negro, may be affected. The apparent greater incidence at times noted among members of a given race in a given country is in reality due to other causes. Among animals certain species of fishes appear to be very resistant to it.

Sex.—During childhood the incidence of endemic goiter is about equal among boys and girls. From puberty onward, the female sex is most often affected, the ratio varying from 2:1 to 6 or 8:1, according to the statistician. Puberty and gestation predispose to goiter. Goiters may enlarge greatly during pregnancy, usually diminishing in size afterward, although in a number of cases, pregnancy in normal women is known to cause hypertrophy of the thyroid. Even menstruation may cause swelling of the gland. The sex incidence is much influenced by the severity of the endemic. In lightly

affected communities women are more susceptible; but when the disease is very severe, both sexes may be equally attacked.

Age.—In regions where the incidence of endemic goiter is high, the disease is not uncommon in breast-fed infants. In certain Himalayan villages, for example, as many as 60 per cent of them have been found to be goitrous. In these cases the disease is congenital.

The incidence of the disease in children varies in different endemic areas, and appears to be largely dependent on the duration of the epidemic in any given locality, and on the degree of natural resistance to the disease acquired by the indigenous inhabitants. In some regions where goiter has prevailed for centuries, visible goiters are comparatively rare in indigenous children under eight years of age. In others, where the disease has been introduced more recently, its incidence in children of all ages is often very high, and in a locality where it is beginning to prevail, cases are found chiefly among children.

When children are subjected to goitrigenous influences for the first time they are considerably more susceptible than adults. The most susceptible age is nine years in the case of boys, ten years in the case of girls. After the tenth year the susceptibility diminishes slightly until the onset of puberty when it increases again, especially in girls.

With increasing age, the susceptibility to goiter gradually diminishes in males, but increases in females during the childbearing period of life. Goiter rarely develops after the age of forty-five years, when the physiologic atrophy of waning life commences. When goiter does develop at this age, it is not, as a rule, due to hyperplasia, but to adenomas, or, more rarely, to malignant disease.

"*Exophthalmic goiter.*—This disease was recorded in 8,647 cases, of which 3,684 were from urban districts and 4,963 from rural. The ratio for rural districts was 2.80, and for urban 3.76. This gives a proportion of rural to urban of 74 to 100 for this disease. Inquiring into the significance of this defect, we have first to note that it is relatively uncommon in New York City (2.78), in Philadelphia (2.12), and still more uncommon in Boston (0.56), whereas it is exceedingly common in Chicago (8.59). It is clear, then, that the high urban rate is not a characteristic of cities as such, but it is due to the presence in certain cities, of conditions especially inciting to this disease or of a population peculiarly liable to it. In comparing the incidence of exophthalmic goiter in the different states we find that there is less of it in the southern states of Texas, Arkansas, Florida, Louisiana, Alabama and Mississippi. These constitute part of the great rural area of the country. On the other hand, the more densely populated states of Michigan, Illinois, Pennsylvania, and Ohio come toward the top of the list. However, it is clear that it is not density alone which determines the order of the states, since Massachusetts is third from the bottom and Rhode Island and Connecticut are in the lower third of the series. One reason why the southern states have such a small proportion of exophthalmic goiter is because of the negro population. However, in the black belt the rate for exophthalmic goiter is only 0.99, and even in the south outside of the black belt it is 1.60, while in the northern agricultural districts the ratio is 3.95 and 4.95 for section 1 and section 2, respectively. Indeed, the eastern manufacturing district has a smaller rate for exophthalmic goiter than have the

agricultural districts of the north. But is it not solely due to the absence of a negro population that Wisconsin, Michigan, and Oregon stand so high in the series of states with exophthalmic goiter? Examination of the map shows that the whole district around the Great Lakes and the extreme northwest are districts of high incidence of exophthalmic goiter, whereas both urban and rural districts in the east are relatively free from it. We conclude, therefore, that there is something in the conditions of the region referred to which tends to produce exophthalmic goiter.

"*Simple goiter.*—This disease was found in 11,971 cases of which 4,289 were from urban districts, and 7,682 from rural. The ratios are respectively, 4.37 and 4.32. In other words, the rural rate is 99 to urban 100. Simple goiter is seen to be somewhat commoner than exophthalmic goiter in rural districts. Also, ratio of occurrence is much smaller in the large cities than is that of exophthalmic goiter. Thus, for example, for New York City the ratio is 0.76; for Philadelphia, 1.11; for Boston, 0.20; and for Chicago the rate is 11.51. We see, then, that the rate for the great eastern cities is less for simple than for exophthalmic goiter, whereas for Chicago the rate is even greater than for exophthalmic goiter, and is more than fifty times as great for Chicago as for the city of Boston. The distribution of simple goiter in the different states is a good deal like that of exophthalmic goiter, but is even more concentrated in the states of the northwest and the Great Lakes. For the southern states, the rate is small, and is relatively low as compared with exophthalmic goiter for the densely populated states of Ohio, Pennsylvania, and New York. As in the case of exophthalmic so in the case of simple goiter, the black belt of the south is relatively free from it whereas the agricultural regions of the north have relatively far more of it than of exophthalmic goiter, and the agricul-

tural section which is occupied by a mixture of foreign and native whites has a much higher incidence than that occupied by native whites primarily. It is clear that certain European races are characterized by an extraordinary rate of simple goiter. Thus, in the group of sections occupied by 10 per cent Finns or over, we have a rate of 20.3, but this may be because the Finns occupy mountainous districts. However, the Scandinavian rate is 13.22 and these are mostly agriculturists; but both the Finns and the Scandinavians are found in the northwest, where there is reason for thinking that the environment conditions tend to increase the amount of simple goiter. The end-result of this complex of causes is, then, the practicable equality that there is between urban and rural districts. On the one hand, the rural rate is depressed by the low rate in the agricultural areas of the south, especially those occupied by Negroes. On the other hand, the rural rate is raised by the high incidence of simple goiter in the great agricultural territories of the north and central west. The urban rate is raised by the high incidence in Chicago and other cities of the Great Lakes region, but it is depressed by the extraordinarily low rate in the great cities on the Atlantic coast, where those conditions which incite goiter in the Great Lakes region and the northwest seem to be largely absent."

The Parathyroids

Pineles, on the strength of his clinical researches on congenital absence of the thyroid, came to the conclusion that the parathyroids and thyroids were entirely different organs, anatomically as well as functionally.

According to various authors there may be as many as from five to twelve parathyroid glands, although four is the usual number. The position of these glandules may vary within certain definite limits. The superior

parathyroids are more constant in position than the inferior ones. The superior parathyroids are found, one on each side, in the vertical groove between the esophagus and the thyroid at the junction of the upper third with the lower two-thirds of the thyroid gland; this is about at the level of the cricoid cartilage. As a rule they are wholly outside of the glandular capsule. The arterial branches and the inferior laryngeal nerve pass up in front, and internally, to them. The inferior parathyroids generally lie more laterally than the superior ones. They are located at the junction of the lower third with the upper two-thirds of the thyroid and are external to the inferior laryngeal nerve and the inferior thyroid.

In most cases both the superior and inferior parathyroids get their blood supply from a branch or division of the inferior thyroid artery through a small vessel called the parathyroid artery. Only rarely does the superior thyroid artery give off a branch destined for the superior parathyroids; in such instances these two small parathyroid arteries, the one destined for the superior parathyroid and the other destined for the inferior parathyroid, may anastomose together. In certain cases both the superior and inferior parathyroids get their blood supply independently from a small collateral blood vessel coming off directly from the posterior longitudinal anastomosis which runs on the inner posterior border of the thyroid gland and connects the superior with the inferior thyroid arterial system.

Between the parathyroid and the thyroid capsule there is a fine collateral circulation. Another collateral circulation, mainly from the superior parathyroids, is secured by fine arteries coming from the pharynx, esophagus, and trachea. Furthermore, Ginsberg has shown that the secondary blood supply for the para-

thyroid glands is secured by anastomotic channels from the opposite side.

Although Pineles was the first to note that the thyroid and parathyroids seemed to be different organs, Gley, Vassale and Generali deserve the credit for proving that all the symptoms observed in animals after strumectomy did not have the same origin, and that nervous symptoms and convulsions were due to an injury of the parathyroids, whereas myxedema was caused by a thyroid insufficiency.

Tetany occurs after total extirpation of the parathyroids, although not after partial extirpation; no lesions of the nerves in the neck, no matter how extensive and complicated, can determine similar symptoms; furthermore, the parathyroids are histologically different from the thyroid. If the thyroid alone is removed, myxedema follows but no tetanic convulsions. If the parathyroids are removed and the thyroid is left untouched, the clinical picture of parathyroid insufficiency at once becomes acute, but no myxedema follows. Trophic disturbances are due to the absence of the thyroid alone, whereas acute, convulsive troubles must be referred to the suppression of the parathyroid function. Furthermore, in athyroidism the thyroid function alone is suppressed, whereas the parathyroid function remains normal. Finally, parathyroid opotherapy is often capable of curing tetany, whereas thyroid opotherapy is inefficacious.

Our knowledge regarding the function of the parathyroid glands may be summarized as follows:

1. In many species of animals the removal of all parathyroid tissue causes death from tetany, within a few days in most instances; the herbivora are less susceptible to tetany than the carnivora; age appears to have a definite influence on its frequency and severity as probably also do pregnancy and lactation. There is some

evidence of late trophic changes in animals that survive parathyroidectomy and have few or no tetanic symptoms.

2. The preservation of very small amounts of parathyroid tissue either prevents tetany or renders it less intense.

3. The function of the parathyroids appears to be distinct and separate from that of the thyroid; the parathyroids are not embryonic thyroid tissue, and the only relationship between the glands seems to be anatomic.

4. There is evidence that the function of the parathyroid glands is in some way concerned with calcium or guanindin metabolism or with both; they may play some part in the regulation or maintenance of the acid-base equilibrium in the body.

5. The experimental evidence pointing to the parathyroids as the primary cause of idiopathic tetany, unassociated with operative procedures on the thyroid, is very limited.

6. The only definite clinical entity which has yet been proved experimentally to be of parathyroid origin is the tetany occasionally seen after operations on the thyroid. In these conditions calcium in large doses usually ameliorates the symptoms. The reports as to the benefit obtained by parathyroid transplantation or feeding are not convincing.

The Total and Nitrogenous Metabolism in Exophthalmic Goiter

"Friedrich Müller, in 1893, demonstrated a general increase in metabolism in exophthalmic goiter by showing that a patient with this disease lost weight and nitrogenous substances on a diet more than sufficient to prevent such losses in a normal individual. Since that time the conception has been prevalent that the increase in the basal metabolism is generally accompanied by,

and even dependent on, an increase in the rate of destruction of the patient's own protein tissue. However, as shown by the studies of Magnus Levy, of Falta and of Du Bois, who likewise have presented summaries of the subject, an increased protein destruction does not always occur, and these authors are rather guarded in their conclusions.

"On account of the importance of a correct understanding of the total and the nitrogenous metabolism in exophthalmic goiter, from both the practical and the theoretical points of view, it was thought advisable to reinvestigate the subject. For this purpose a small metabolism ward of four beds was established adjoining the metabolism laboratory, and with its own special diet kitchen. In this ward nine patients, who had marked and unquestionable exophthalmic goiter, have so far been studied. The food was prepared from known recipes, the ingredients of which were weighed, and its protein, fat, carbohydrate and total calory value calculated from Atwater and Bryant's tables. In the later experiments, some of the principal items comprising the diet were analyzed for nitrogen by the Kjeldahl method; the fats were determined by ether extraction and the carbohydrates estimated by difference from the determination of the total calorific value found by combustion in a Parr adiabatic bomb calorimeter. As considerable use was made of "40 per cent" cream in the construction of the diet, the cream was analyzed daily for the fat content by the Babcock method. All food not eaten was reweighed, and the corresponding calories were deducted.

"Every effort was made to insure the completeness of the twenty-four hour urine specimen. Male subjects are greatly to be preferred, not only on account of ease in collecting the entire quantity of urine, but also because the loss of nitrogenous material at the time

of menstruation is avoided. Each day the total nitrogen of the urine was determined by the Kjeldahl method, and the urea nitrogen, ammonia nitrogen, creatinin, uric acid and sugar by the Folin method; occasionally the amino-acid nitrogen (Folin) was likewise determined. On each patient a complete blood analysis by the Folin system was made at short intervals throughout the period of investigation. The basal metabolic rate and respiratory quotients were determined in duplicate periods each day, except immediately after operation by the open or gasometer method, with analysis of the expired air according to the technic that we have previously described. The feces were not analyzed, nor was any attempt made to determine the quantity of nitrogen lost by sweating or desquamation. In calculating the nitrogen balance, 10 per cent of the food nitrogen was added to urinary nitrogen, and the result assumed to be the total nitrogen elimination.

"In reviewing the accuracy of our data as regards the nitrogen ingested and eliminated, it seems probable that the average error in the nitrogen balance is approximately 1 gm.; only occasionally can this error materially exceed 2 gm. The error was estimated as follows: no material error occurs in the Kjeldahl determination or urinary nitrogen, and accidental errors were excluded by making duplicate determinations. With the precautions taken in collecting the urine, it would be impossible in any case to lose more than 10 per cent, while in the greater number it is unlikely that the loss, on the average, exceeded 1 per cent. The estimation of the fecal nitrogen at 10 per cent of the food nitrogen is probably in most cases correct within plus or minus 5 per cent; it certainly would not exceed 20 per cent of the food nitrogen in any case. Although patients with exophthalmic goiter perspire freely, only occasionally is the skin more than moist, even in summer

time, under conditions of resting in bed, so that the error produced by neglecting this factor, could not, according to the available date on skin elimination, exceed on the average 0.1 gm. daily. Such precautions were taken in analyzing important items of the food, and in preparing and weighing the diet, that an error in the estimation of the nitrogen of food could hardly exceed plus or minus 10 per cent of the total, and for the long periods studied it seems highly probable that the average error would be much smaller. While the sum of all these errors may be slightly more than 2 gm. yet they will rarely be all in one direction, and will thus offset one another.

"The outstanding and essential fact is that, on a protein intake varying between 34 and 136 gm., it was impossible to maintain at least nitrogen equilibrium, and usually to obtain a positive nitrogen balance well in excess of the probable maximal experimental error, provided sufficient carbohydrate and fat were likewise administered. On account of the decreased weight of the subjects, the protein intake varied, as a rule, between 1 and 2 gm. for each kilogram; in a few instances, a little more than 3 gm. for each kilogram was given. The proportion of protein was, however, very low when compared with the mass of food taken, and it proved exceedingly difficult to provide large, appetizing diets, which would appeal to the patient for many days, with less protein than was used in the majority of instances. Even those diets containing more than 100 gm. of protein would, if based on the amount of food ordinarily served to hospital patients, have a protein content in the region of 50 gm.; for example, the 136 gm. of protein in 5,403 calories of the first period for Case 3 would be equivalent to only 50 gm. in a 2,000 calory diet.

"There was only occasionally a negative nitrogen balance; this was unimportant if it occurred immedi-

ately following a sudden and marked reduction in the protein intake, but might be of more fundamental significance if it occurred as a result of a gastro-intestinal crisis." (Boothby and Sandiford.)

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THE FUNCTION OF THE THYROID GLAND

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Kendall separated thyroxin as a pure chemical compound in 1914, determined its empirical formula in 1917, and proved its structural formula in 1918.

The chemical reactions carried out by thyroxin in the tissues are not known. The chemical and physiologic properties of thyroxin indicate that it is used directly in the processes of oxidation as a catalytic agent. The following hypotheses led, in 1917, to the quantitative physiologic determinations that are given in succeeding paragraphs, and from the dynamic standpoint offer a concept of the action of this agent that may at least approximate the truth.

1. Thyroxin is active in nearly all or all the cells of the body.

2. Thyroxin is a catalytic agent hastening the rate of formation of a quantum of potential energy available for transformation on excitation of the cells.

More recently, Kendall has demonstrated that thyroxin increases the intensity at which oxidation of hydrogen occurs, which is in accord with the preceding hypothesis based largely on clinical observation.

The following quantitative determinations based on the intravenous administration of single large and daily small doses of thyroxin to patients without thyroid function are probably approximately correct:

1. The amount of thyroxin in the tissues of the average normal adult man is 14 mg.

2. The thyroid delivers approximately 0.33 mg. of thyroxin daily. This amount probably varies with the metabolic activity of the organism.

3. Until levels considerably above the normal are reached, 1 mg. of thyroxin elevates the basal metabolism 2.8 per cent.

The function of the thyroid is to maintain 14 mg. of thyroxin in the body, or to elaborate and deliver 0.33 mg. of thyroxin daily. It may have many unknown functions.

Although we know but little regarding the stimulating mechanism which causes the thyroid to discharge thyroxin, we can assume that it is normally brought into play by potential or actual hypothyroidism. We can almost as readily assume the converse of this, namely, that the administration of sufficient thyroxin to maintain 14 mg. in the body will place the thyroid at rest. Oral administration suggests that this assumption is correct.

The normal thyroid can be largely resected before diffuse hypertrophy of the remnant will occur, although it will continue to deliver the normal amount of thyroxin. This indicates that the diffuse hypertrophic thyroids of endemic goiter and exophthalmic goiter are intensively stimulated, and that stimulation above the normal should, acting on a normal thyroid, cause hyperthyroidism before diffuse hypertrophy takes place. Diffuse hypertrophy is in general an index of intensive or sustained stimulation. It is self-evident that a supply of iodin inadequate for thyroid function will result in hypothyroidism and intensive or continued stimulation. It is self-evident that intensive stimulation acting on a primarily normal thyroid will cause hyperthyroidism. From this point it is easy to step to the hypothesis that intensive stimulation of the primarily normal thyroid, having a relative, to the degree of stimulation, inadequate supply of iodin, will cause the delivery of an abnormal product, characteristic of the physiologic status of exophthalmic goiter.

That new tissue may develop in an organ under stimulation is a common observation, but that this new tissue should function and elaborate a normal product far in excess of the requirements of the organism, as seems to be the case in the thyroid, is unique.

Classification of Goiter

The normal thyroid is composed of vesicles lined with cuboidal or low columnar epithelium supported by the sustentacular tissue common to gland structure. To go further into the histology of the normal thyroid leads, on the whole, into detail relatively little of which can be correlated with pathologic conditions or which is, at least, confusing to the average reader.

Three departures from the preceding somewhat conventional picture of the normal thyroid dominate a study of the relationships of anatomic changes in the thyroid to its functional activity, and form the basis for the anatomic classification for the diseases grouped under the term "goiter." They are: (1) hypertrophy of the vesicular epithelium, (2) fluctuations in the amount of colloid stored in the vesicles, and (3) the development of groups of new acini.

The evidence of fluctuation in the blood supply and of the destructive effect of thyroiditis are almost of equal importance in the correlation of clinical conditions, functional activity and the histologic changes in the gland.

Pure types of goiter may be classified anatomically as diffuse hypertrophic, diffuse colloid, and adenomatous. The localization of these processes and their frequent admixture in the same thyroid cause much confusion in the classification of goiter as well as in the study of functional relationships.

In this article, hypertrophy is applied to an increase in the size of the cells of the vesicular epithelium, and hyperplasia to an increase in the number of cells in each

vesicle. The term "adenomatous goiter" or "adenomatous thyroid" is applied to those thyroids in which there is an abnormal increase in the number of new acini. It should be borne in mind that the terms "hypertrophy" and "hyperplasia" are used with quite different meanings in the literature on the thyroid. For instance, hyperplasia is frequently used to include both an increase in the number of acini as well as in the number of cells in individual acini, and the term "hypertrophic" has been applied to all types of goiter.

In terms in common use in American literature, the best grasp of the subject can be obtained by classifying goiters as endemic and exophthalmic. The endemic goiters may be divided into the diffuse colloid and the adenomatous; and the adenomatous into those with and those without hyperfunction. This classification probably rests on a definite etiologic basis, and it is probable that all or nearly all goiters can be included in the two groups. The most essential known factor in the cause of endemic goiter is a relative or absolute deficiency of iodin for normal thyroid function. With regard to the cause of exophthalmic goiter, although some possible contributing factors can be pointed out, little is known concerning it. In the development of endemic and exophthalmic goiter, a definite etiologic and histologic sequence can be conceived as taking place.

Endemic Goiter.—A supply of iodin inadequate for the proper functioning of the thyroid, followed by a subnormal delivery of thyroxin to the tissues, produces hypothyroidism; consequent elevation of intensity of thyroid stimulation causes diffuse hypertrophy of the thyroid; the secretory processes are altered; the diffuse hypertrophy disappears; colloid is stored in excess of the normal, and diffuse colloid goiter is the result. In many cases the sustained stimulation of the thyroid, in conjunction with unknown factors, causes the develop-

ment of new tissue, adenomatous goiter. Relatively late in the life history thyroids containing this tissue in many instances hyperfunction, and the entity hyperfunctioning adenomatous thyroid appears.

Exophthalmic Goiter.—Intensive stimulation, of unknown origin, of the entire functionally capable and probably primarily normal thyroid causes diffuse hypertrophy; an abnormal amount of thyroxin and an abnormal thyroid product is delivered; during periods of remission of intensity of stimulation and an adequate iodin supply, the diffuse hypertrophy disappears in some instances and colloid above the normal amount is stored. Under the stimulation, acini which are possibly more or less new, as a rule, develop. In exceptional cases the gland, particularly after a portion has been resected, becomes much larger from the development of new tissue. This should be sharply distinguished from the adenomatous tissue frequently present before the onset of exophthalmic goiter. In the Mississippi Valley where the incidence of endemic goiter is high, about 30 per cent of the cases of exophthalmic goiter are superimposed on adenomatous goiter.

If the preceding concepts are approximately accurate, it is evident that there are phases in the history of both endemic and exophthalmic goiter when the condition of the gland can be anatomically diagnosed diffuse hypertrophic, diffuse hyperplastic, diffuse colloid, or adenomatous goiter, or a combinatoin of these. This brings out some of the fallacies in nomenclature of thyroid diseases; however, usage makes the classification of goiters into endemic and exophthalmic, the endemic being divided into diffuse colloid and adenomatous, the most practical one for clinicians at the present time. Recognition of diffuse hypertrophy as only an evanescent phase of endemic goiter of man, rarely, if ever, coming under the observation of the physician, partially clears

the field; the absence of diffuse hypertrophy is an almost equally evanescent phase in exophthalmic goiter.

Diffuse Colloid Goiter.—Under the term "diffuse colloid goiter" the clinician groups those cases of endemic goiter in which the enlargement of the thyroid is largely due to the storage of an abnormal amount of colloid in primarily normal vesicles. There is not at present much ground for excluding any cases of diffuse colloid goiters from the endemic group except the rare cases associated with hyperthyroidism that probably constitute part of the exophthalmic goiter entity. Endemic goiter may be congenital. Its incidence is higher in infancy than in later years of childhood. It is much more common in females than in males. Pregnancy is a contributing cause. The enlargement in pregnancy, whether of adenomatous tissue or of the entire gland from the storage of colloid, is evidence of response of a functionally damaged gland to stimuli originating in an increased rate of exhaustion of thyroxin in the body. This is irrespective of the basal metabolic rate.

In the majority of cases diffuse colloid goiter is first noticed during the latter half of the second decade of life. In the United States, colloid goiter usually disappears before the twenty-fifth year; however, there is a tendency for a thyroid once overloaded with colloid, irrespective of its functional activity, to retain more than the normal amount of colloid, sufficient in many instances to make the gland easily palpable throughout life.

Palpable thyroids after the twentieth year, as a rule, contain some adenomatous tissue. It should be borne in mind that in many instances the clinician, and in a certain percentage of cases the pathologist, cannot determine the relative part that diffuse colloid and adenomatous tissue contribute to the thyroid enlargement. Diffuse symmetrical enlargement, conforming to the

shape of the normal thyroid, in patients under the twentieth year without hyperthyroidism, indicates in most instances diffuse colloid goiter, or diffuse colloid goiter with adenomatous areas. Thyroids showing diffuse colloid goiter without adenomatous tissue, with lateral lobes 6 cm. in diameter when picked up and compressed between the thumb and fingers, sufficient for the palpator to be definitely conscious of the mass, are relatively rare in the United States. In what may be considered a typical high grade case, the goiter is first noticed at puberty; it progresses with remissions for from three to five years, and then regresses till it is barely palpable, or at least of relatively small dimensions, before the twenty-fifth year. Spontaneous recovery after a relatively short course is the rule, at least in this country. Bruit and thrill are frequently present in the superior thyroid arteries. The largest thyroid vessels and most notable thrill and bruit on palpation coming under my observation have been in cases of colloid goiter. These are of much interest because of the possible significance of their disappearance within a few hours after the administration of thyroxin and because of the fact that they have frequently, in conjunction with cardiac neurosis often induced by watchful mothers and physicians, led to a diagnosis of exophthalmic goiter and thyroidectomy.

There is much evidence on which to infer that all cases are relatively or absolutely hypothyroid, at least during the period in which the etiologic factors are active. Many patients at the time of coming under observation have a coloration and dryness of the skin and a listlessness indicative of hypothyroidism, which disappears when the basal metabolism is brought to normal by the administration of desiccated thyroid. In a large percentage of the cases coming under my observation the basal metabolism is below the average normal.

The percentage cannot be definitely stated, as in many instances it has been impracticable to hold the patients for a sufficient number of tests. Not infrequently the first, second, third or even the fourth rates are near normal and subsequent rates 10 to 18 per cent below the average normal. No patient with colloid goiter and a basal metabolic rate of more than 18 per cent below normal has come under observation. As far as I know, these patients never ultimately develop myxedema. In a large series of myxedematous cases no patient could give a history of having had diffuse colloid goiter or any other type of goiter to which the myxedema could be attributed.

The use of iodin in the treatment of goiter dates back into ancient history. It has been on a more or less rational basis since its presence in the thyroid was discovered. Reduction in the size or disappearance of colloidal goiter occasionally follows the administration of iodin within a sufficiently short period to warrant attributing the change to this element. However, in many cases colloid goiter is not appreciably changed by its administration for a period of many months. These conflicting results suggest that, but for some unknown factor in the function of the colloid thyroid, iodin would always cause a marked reduction in the size, or the disappearance of the enlargement.

The work of Marine and Kimball, demonstrating that the administration of iodin during childhood and adolescence prevents the development of the diffuse colloid goiter of man, has led to the general acceptance of the hypothesis that a deficiency of iodin in the water and food is the chief factor in the cause of endemic goiter. This work seems to have been stimulated largely by the demonstration by Marine that hypertrophy and hyperplasia precede diffuse colloid goiter in animals and that iodin prevents this cycle of changes. That in

some instances of diffuse colloid goiter the thyroid reduces rapidly in size following the administration of desiccated thyroid has been known almost since the activity of this agent was discovered.

In 1914, speculation as to the significance of the large superior thyroid arteries, evidenced by palpation, bruit and thrill, which were occasionally observed in large colloid thyroids, led me to the hypothesis that the increased blood supply attended an intensive stimulation of the thyroid originating in a hypothyroid state and hence that the administration of desiccated thyroid should stop the stimulation and bring about a reduction in the blood supply. The administration of thyroid in large doses demonstrated that the bruit and thrill in all cases disappeared within from twenty-four to thirty-six hours with marked reduction in the size of the thyroid. The results from this were so satisfactory that since that date the large thyroids of diffuse colloid goiter crowding the superior thoracic strait, causing dyspnea, have not been operated on. It was not until basal metabolism estimations were available in 1917 that almost invariably satisfactory results followed the treatment of colloid goiter. Since then I have treated all colloid thyroids, of sufficient size to warrant the effort, by holding the basal rate at or a little above normal. At intervals of from three to six months the desiccated thyroid is stopped and the patient given from 5 to 10 drops of Lugol's solution daily. If the thyroid again becomes distended with colloid, administration of desiccated thyroid is resumed for another period; if not, the Lugol's solution is continued for a few months. Still later, if the enlargement reappears, the desiccated thyroid is again administered. Very large vascular colloid thyroids may shrink one-third in volume in twenty-four hours, and the remaining still very large goiter may almost disappear in two weeks, although a longer period is as a rule neces-

sary. I have not seen a case in which a sufficient enlargement remained to warrant thyroidectomy. In many instances, and at first seemingly pure colloid thyroid shrinks down rapidly within a few hours or days and reveals the presence of multiple adenomas. In such cases, the thyroid is resected with much more ease and less chance of removing too much of the gland. Too extensive resection of a large thyroid in cases of diffuse colloid goiter, in most instances containing some adenomatous tissue, may cause or increase hypothyroidism and recurrence of distended colloid masses, up to 6 by 10 cm., which rapidly reduce in size and in some cases disappear within a month following an elevation of the basal metabolism to normal. These masses rapidly refill with colloid if the administration of thyroxin is stopped. Following the administration of thyroxin, the remnant of colloid-distended thyroid often present in cretins and patients with lingual goiter rapidly reduces in size.

The facts brought out in the foregoing warrant the working hypothesis that the thyroid functioning with a relative or absolute deficiency in iodin fails to maintain the normal amount of thyroxin in the body; the hypothyroidism brings into action the mechanism which normally stimulates the thyroid; the continuous stimulation acting on the thyroid deficient in iodin is the immediate cause of the anatomic changes in diffuse colloid goiter. It is important to bear in mind that there are objections to this hypothesis and that, if it is approximately correct, the deficiency of iodin in the food and water intake is relative.

The average daily intravenous administration of thyroxin required to hold the basal metabolism of a thyroidless adult at normal is less than 0.5 mg. This is equivalent to approximately 100 mg. of iodin each year, which only indicates the small amount of iodin required for thyroid function. For a discussion of the optimal

intake of iodin and the methods of administration advisable for the prevention of colloid goiter, the reader is referred to the writings of Marine and Kimball. The age at onset of adenomatous goiter and colloid goiter as well as many other observations warrants the inference that the two conditions have a common cause, and hence that iodin will prevent the former as well as the latter. However, direct proof of this is not yet available. As demonstrable adenomatous tissue is developed in only a percentage of cases of endemic goiter it is evident that there is some unknown etiologic factor determining the advent of new tissue in the thyroid.

Kocher made the observation that patients with endemic goiter were prone to develop hyperthyroidism following the administration of iodin, and reported occasional benefit from its use in exophthalmic goiter. He, however, did not, at least not clearly, distinguish hyperfunctioning adenomatous goiter from exophthalmic goiter and hence later advised against the use of iodin. Since then, many men have made similar observations and the teaching of Kocher has been generally accepted. Since I first attempted to separate hyperfunctioning adenomatous goiter from exophthalmic goiter, I have elicited the fact that the administration of iodin preceded hyperthyroidism in a sufficient number of cases of hyperfunctioning adenomatous goiter to warrant inferring an etiologic relationship. This could not be done in a sufficient number of cases to warrant the same assumption for exophthalmic goiter. Not infrequently I elicited a history of hyperthyroidism of months' or years' duration although iodin had been administered for only a few weeks at the onset. The syndrome was the same as that in the majority of the patients with hyperfunctioning adenomatous thyroids who had not taken iodin. This led to the teaching that iodin helped to initiate hyperfunction in cases of old adenomatous goiter, but that

once this was started, it continued as a rule much the same as in the cases in which the iodin in the food is sufficient for the onset of excessive function. I am still of the opinion that the administration of iodin causes adenomatous thyroids to hyperfunction; that it does, however, is an inference, not an established fact. There is little, if any, evidence on which to assume that the administration of iodin will cause an increase in the degree of hyperthyroidism once hyperfunction has started; however, hypotheses urge caution. A hyperfunctioning adenomatous thyroid under the twentieth year is a curiosity. I have seen hyperfunction follow the administration of iodin in adolescence, but so infrequently that there seems to be no practical objection to giving it in cases of adolescent goiter, which is frequently a combination of diffuse colloid and adenomatous goiter. The clinician cannot ever be sure that the latter is not present. Will the small doses of iodin required for the prevention of adolescent goiter increase the prevalence of hyperfunctioning adenomatous thyroids if it is universally included in the diet of adults? Nobody can answer this question, perhaps no one ever will, although many will soon make the attempt on inadequate data. I have seen many patients with adenomatous thyroids who gave a history of onset of hyperthyroidism since beginning the use of iodized salt; however, this alone does not even suggest an etiologic relationship.

Adenomatous Goiter.—Little is known regarding the duration of the normal life of the vesicles and the systematic development of new vesicles to replace those exhausted. The interest of the clinician and pathologist centers largely in the development of groups of new acini that cannot be considered normal. Woefler contributed much to the subject of adenomas of the thyroid, and made the observation that they develop from fetal rests. That anyone has actually traced the develop-

ment of new acini from embryonal tissue is open to question. The groups of new vesicles may be very circumscribed and few in number, or distributed widely throughout the gland. The tissue may be encapsulated (true adenoma) or nonencapsulated (adenomatosis). In many cases a sharp distinction between encapsulated and nonencapsulated tissue cannot be made. That there is some difference in the factors entering into the histogenesis of nonencapsulated adenomatous tissue, widely distributed throughout the thyroid, and circumscribed encapsulated adenoma cannot be questioned. Under the terms "adenomatous tissue" or "adenomatous goiter" both types are included. In some adenomatous tissue, vesicles in all stages of development may be observed. The lumina of the so-called fetal acini contain no colloid and the cells present the general appearance of not having functioned. The fully developed new vesicles show the same histologic evidence of function as the normal vesicles and hence cannot be distinguished individually from the vesicles of the surrounding normal gland tissue. Depending on the relative number of adult vesicles, adenomas are classified as fetal or adult. In many adenomas a high percentage of all the vesicles contain colloid and the new tissue is termed colloid adenoma. An isolated section of such tissue may not be distinguishable from the surrounding normal or colloid-distended thyroid.

All the nodules in some thyroids, resected in hyperthyroid or nonhyperthyroid cases, are not encapsulated and contain few, if any, acini of the fetal type. The histogenesis of these nodular thyroids, in which the vesicles of the nodules all or nearly all contain colloid and are not encapsulated, is open to question. Whether certain of these nodules are due to a localized deposit of colloid in primarily normal vesicles or to an advanced stage of adenomatosis, in which the acini have lost their

fetal characteristics, is a crucial point in the study of the relationship of histologic changes to function and the classification of nodular goiters. But for this question, adenomatous goiter and nodular goiter are terms that might be used almost synonymously. The gradation from one type to the other may be observed in the nodules of an individual gland. In the routine daily report of the tissue removed at operation, MacCarty classifies these not definitely encapsulated nodules with the adenomatous thyroids. On his reports the statistics giving the incidence of adenomatous goiter are based. The clinical evidence is perhaps of more significance than the histologic study. Without going into detail, it is sufficient to say that, in general and so far as the investigation has been carried, nodular thyroids have, irrespective of the presence or absence of fetal acini or encapsulation, the same life history and the same tendency to cause hyperthyroidism. Again, following enucleation of the nodules, irrespective of type, the basal metabolism of the patient if previously elevated drops to normal in three weeks.

Two theories prevail regarding, hyperfunctioning adenomatous thyroid: first, that the adenomatous tissue elaborates and delivers an excess of thyroxin; and second, that it in some way stimulates the surrounding thyroid tissue to hyperfunction. Although the questions must still be considered open, the evidence accords best with the theory that the adenomatous tissue hyperfunctions. To avoid this question in goiter classification, I have used the term hyperfunctioning adenomatous goiter which, so far as this point is concerned, is noncommittal. Irrespective of the question of which type of tissue furnishes an excess of thyroxin, there is no doubt that the adenomatous tissue actually elaborates thyroxin and stores colloid and iodin. In the following discussion of adenomatous goiter, the facts may be coördinated with

either theory; however, I have assumed that the adenomatous tissue hyperfunctions.

In most cases adenomatous goiter has its inception in colloid goiter. The embryonal cells seem to be stimulated through the same mechanism that forces the gland to maintain a normal level of thyroxin in the tissues. Possibly we should look on adenomatous tissue somewhat as a compensatory attempt. Such a theory does not eliminate the possibility that the formation of the new tissue may in some or all instances be determined by local irritants. Early in its life history adenomatous tissue cannot function. A number of observations suggest that it can elaborate and store colloid long before it can elaborate and store thyroxin. Only rarely are the factors such that the adenomatous tissue will function, at least to the point of causing hyperthyroidism, before the latter half of the third decade of life, although as a rule, it is palpable in the second decade. Only 5 per cent of the hyperfunctioning adenomatous thyroids coming under observation at the Mayo Clinic are in patients under thirty years of age. These constitute about 5 per cent of all adenomatous thyroids resected in patients under the thirtieth year. Sixty per cent of all adenomatous thyroids, resected in patients after the sixtieth year of life, are hyperfunctioning. The average interval between the time the goiter is first noticed and the onset of hyperthyroidism, including only those that hyperfunction before coming under observation, is seventeen and six-tenths years. Although the normal stimulating mechanism seems to be a factor in the inception of adenomatous goiter, once this tissue has started to function it does so erratically without relation to the demands of the organism. This observation is borne out by the fact that the basal metabolism drops to normal, but not below, within eighteen days after resection of the adenoma-

tous tissue and there is no tendency to a recurrence of the hyperthyroidism.

It may readily be conceived that in this postnatally developed tissue the mechanism for coördinating its functional activity with the demands of the body is not fully developed. There is no apparent reason for the onset of hyperthyroidism in the majority of cases. It may be inferred that the adenomatous tissue has an inherent tendency to hyperfunction which is favored by various factors. The increased rate of exhaustion of thyroxin and the resulting elevation in the intensity of stimulation of the thyroid, which we have reason to assume exist in conditions such as essential hypertension, pregnancy and pituitary disease, probably favor the development of adenoma and not infrequently excite adenomatous thyroids to hyperfunction. In these cases the tendency to store colloid is, in general, inverse to the tendency to hyperfunction.

The treatment of hyperfunctioning adenomatous thyroid is essentially surgical. The operative mortality for a long series of years has been approximately 3.5 per cent. The mortality for 1925 was approximately 1 per cent. This drop in the mortality was largely, if not wholly, due to stopping the use of digitalis in cases in which there was auricular fibrillation.

Hyperthyroid States

Hyperthyroidism occurs unquestionably in three states: (1) following the administration of the thyroid gland or its active agent, thyroxin; (2) in persons having hyperfunctioning adenomatous thyroids, and (3) in persons having exophthalmic goiter. There is a small group of hyperthyroid cases with diffuse colloid goiter with or without areas of hypertrophy in which there is not sufficient evidence to classify them either with the endemic goiter or exophthalmic goiter. I am in-

clined to believe that these cases should be included with a group having the same histologic changes in the thyroid and a clinical complex warranting the diagnosis of exophthalmic goiter; however, in an attempt to analyze the hyperthyroid complexes, I have for the present pigeonholed them.

It is possible that mild hyperthyroidism is sometimes present in other conditions, notably, essential hypertension, and certain psychoneurotic states. It is possible that there is, in general, a tendency for the thyroxin content of the body to rise slightly when the basal metabolism is held above the average normal by other dynamic agents, and in the physiologic states more or less attended or induced by an inability of the organism to come to rest. The average rate of exhaustion of thyroxin in normal and near normal periods of stress is probably some coefficient of the total metabolism. Evidence of high functional activity of the thyroid in conjunction with neurotic manifestations is frequently erroneously interpreted as indicating a hyperthyroid state.

The primary clinical manifestations of the hyperthyroid state associated with adenomatous goiter are, or are due to, the reactions that must accompany an elevation of the rate of energy transformation in the body: (1) cardiovascular findings that are indicative of an increased minute-volume flow of blood from the heart; (2) increased surface temperature and perspiration indicative of an elevation of heat elimination; (3) increased food consumption, in most instances insufficient to maintain the body weight, and (4) a group of findings attributable to fatigue. The nervous phenomena are those present in many conditions associated with nervous fatigue, not those characteristic of exophthalmic goiter. On being informed that the basal metabolism is above normal, a physiologist without any

previous knowledge of hyperthyroid conditions might predicate the entire physiologic complex. There is possibly one exception to this, namely, the frequent occurrence of auricular fibrillation.

The following observations make it seem probable that the hyperthyroidism associated with adenomatous goiter is due to an excess of the normal active agent of the thyroid in the tissues of the body: (1) the primary phenomena observed are only exaggerations of normal physiologic reactions; (2) from our knowledge of physiology we can conceive of no simpler reactions occurring with an elevation of the basal metabolism; (3) these reactions return to their normal level in three weeks following the enucleation of an adenoma, and (4) the phenomena in no way differ from those following the administration of desiccated thyroid or thyroxin.

These observations on adenomatous goiter were largely responsible for my conviction that a person with a normal basal metabolism, other factors being normal, is neither hypothyroid nor hyperthyroid, and to the formation, in 1915, of the following working hypotheses: (1) thyroxin is active in nearly all or all the cells of the body, and (2) thyroxin is a catalyst hastening the rate of formation of a quantum of potential energy available for transformation on excitation of the cells.

The complex of hyperfunctioning adenomatous thyroid can be reduced to physiologic terms, hence, can be covered in a few short sentences. That of exophthalmic goiter is fluctuating in character and degree and not as yet wholly reducible to physiologic terms.

The clinico-physiologic complex of exophthalmic goiter can readily be conceived as that following the administration of thyroxin, or that associated with hyperfunctioning adenomatous thyroid plus certain notable characteristic findings that can be grouped as ocular symptoms, the characteristic nervous phenomena, and the tendency

to crises which may terminate in death. To these might be added a number of findings, which, to avoid confusion, will not be considered. Many of these findings are of high value in differential diagnosis, the presentation of which is not the purpose of this paper. There is no intent by omission to belittle the evidence suggesting that the adrenal bodies may play an important part in the physiologic complex. The characteristic findings I attribute to a hypothetical abnormal product of the thyroid.

Ocular Findings.—For the purpose of this paper it is only necessary to divide the ocular symptoms into exophthalmos and the peculiar stare of about 65 per cent of the patients at the time of coming under observation. The stare is frequently present when there is no exophthalmos, and may disappear when there is a high degree of exophthalmos and hyperthyroidism. It fluctuates directly with the other phenomena attributed to the abnormal agent. Prolongation of the factor that gives rise to the stare probably causes protrusion of the eyeball. In clinical analysis, exophthalmos at any given period in the course of the disease should be considered an index of a preëxisting physiologic state that may or may not still be present.

Nervous Phenomena.—The entire nervous system seems to be in a status of hyperirritability and fatigue. The patient is restless, easily irritated, and subject to emotional outbreaks. The picture varies with the duration as well as the degree of intoxication and with certain factors that for brevity may be grouped under the heading "personality." The intoxication is in many ways comparable to acute and chronic alcoholism. Tears and laughter come without the patient's knowing why. As in acute alcoholism, the person may carry a good load without its being evident. Again, it may not be evident unless the person is irritated. Once irritated,

the patient may be as hard to manage as a drunken soldier. Placing the patient in bed in a nonirritating environment benefits the patient but also camouflages the status. The lack of assurance that is so characteristic of psychoneuroses is strikingly absent if the patient is not in an emotional mood, characteristically depressed or fundamentally of a neurotic temperament. The patient frequently complains of an "inward" nervousness, which is the cause of what I have termed purposeful but useless motions. These are sufficiently characteristic to permit of a diagnosis of exophthalmic goiter, on inspection, in at least 60 per cent of the cases. In rapid succession the legs may be crossed and uncrossed, the tie adjusted, a garment buttoned and unbuttoned, and so forth, almost without end. This series of motions may be interspersed with various poses. If the patient is sitting on an examining table, the arms are likely to be thrown back and the hands rested on the table in such a way as to act as a crutch to support the exhausted muscles of the back. The motions are in a way an index of similar psychic reactions. A somewhat comparable status exists in the sympathetic nervous system, which on clinical analysis cannot be completely dissociated from the higher psychic reactions. If the status suddenly disappears, the patient in response to a question as to his condition replies that he has passed into a state of complete repose or makes some similar answer.

In addition to the adjustment of the circulation, heat elimination, and so forth, necessitated by the elevation of the basal metabolism which, as a rule, seems to take place in a well-balanced way in the hyperthyroid state associated with the hyperfunctioning adenomatous goiter, there are evidences of chaotic attempts on the part of the sympathetic nervous system to maintain a

balance in its coördinating function in the metabolic processes.

Crises.—As the degree of intoxication becomes higher and the nervous phenomena become more marked, the patient is likely to thrash about on the bed and develop erythema. The erythema may be general, though more often it is confined to the elbows. This is almost pathognomonic of a high degree of intoxication attributed to an abnormal thyroid product. I have become accustomed to refer to such patients as being on the "verge of a crisis" or "in a crisis status." Vomiting, delirium, and coma often develop in patients living in the Mississippi Valley. Sudden deaths are not infrequent. Death may be precipitated by seemingly slight causes, such as the injection of hot water into the thyroid or ligation of a superior thyroid artery. Such deaths will be referred to as preoperative or postoperative crisis deaths. Postoperative crises are as a rule precipitated in patients showing definite evidence of high intoxication. In some cases, critical study gives relatively little warning. The correlation of facts indicates that many of these patients are highly intoxicated and develop the crises much as an alcoholic does delirium tremens. On the other hand, there is much to suggest that the crises may be in some instances caused or augmented by sudden discharge from the thyroid.

Death.—To analyze accurately all deaths occurring in cases of exophthalmic goiter is impossible. Certain generalizations, as suggested from an analysis of the deaths occurring in Rochester, previous to the use of iodin, may be made. The majority of nonoperative and operative deaths were about equally divided between those occurring in crisis and those from definite infectious processes, such as pneumonia, endocarditis, suppurative cholecystitis, pyelonephritis, and so forth. The relative number of the two groups has varied some-

what from year to year. The study of the relationship of the development of the infectious processes to the exophthalmic goiter syndrome clearly indicates that latent infections become active when a crisis status is present whether this develops spontaneously or is the result of operation.

About one-third of the deaths cannot be included in the crisis group and infectious group just discussed. In this one-third, death can be attributed to such causes as might be intercurrent in other than thyroid disease: cardiac damage; damage to the laryngeal nerves; intensive metabolic reactions in which the entire complex suggests that the thyroid is delivering little, if any of an abnormal product. Death may occur from intensive metabolic reactions that are hard to distinguish from the typical postoperative crisis. The same type of death is occasionally noted in cases of hyperfunctioning adenomatous thyroid. When considered en masse these deaths seem to stand out quite distinctly from the typical crisis death although it is hard to point out any definite difference in some cases. The typical crisis never occurs in cases of hyperfunctioning adenomatous thyroid.

The mortality percentages given in this paper, unless otherwise indicated, are obtained by dividing the number of deaths in any given period by the number of cases in which the first operation for goiter was performed in any of the hospitals associated with the Mayo Clinic, in the period. This gives a higher mortality than if cases in which primary operation had been performed in previous years were included in the divisor, and affords a fairly accurate index of the risk associated with the surgical treatment of exophthalmic goiter. All cases of death in the hospital following injections of hot water, ligations, and resection of the thyroid are included in the operative mortality. In the

nonoperative mortality are included all other cases of exophthalmic goiter in which the patient died in Rochester, irrespective of the immediate cause of death.

The operative mortality rate for the ten years preceding the introduction of the use of iodin has averaged about 3.5 per cent. It has varied but little from year to year except to rise during the recent pandemic of influenza.

The number of nonoperative deaths for the years 1918 to 1922 were respectively sixteen, eighteen, fifteen, ten, and sixteen. During this period the operative mortality in the group of cases coming from the portion of the United States east of a line drawn north and south through the State of Indiana, was less than 0.5 per cent.

Irrespective of other possible differences, I am convinced that the number of cases that will attain a status in which death is imminent, and hence in which it is easily precipitated, is not the same throughout the world. Evidence suggests that the incidence, as well as the number of patients who reach a crisis status, is different in adjacent counties throughout the northwestern states.

An analysis of the mortality in the clinic up to the time the use of iodin was begun showed that any very material reduction in the rate was seemingly impossible unless a radically new departure could be made in treatment. An analysis of the deaths indicated that nearly 3 per cent occurred under such conditions that death could not be attributed to any known errors in operative technic or avoided by any known methods of preoperative management, except possibly waiting for weeks and in some cases for months for the crisis status to disappear, which course would have increased the nonoperative mortality and probably reduced the operative mortality.

Theory of Dysfunction of the Thyroid

In 1912, I pointed out that the physiologic status of patients with exophthalmic goiter is different from that of those with hyperfunctioning adenomatous thyroids, and suggested the theory that the complexes vary with the amounts of three active agents elaborated by the thyroid. I then entertained the idea and soon adopted the working hypothesis that the physiologic complex associated with hyperfunctioning adenomatous thyroid is due to an excess in the body of the normal active thyroid agent, and that the characteristic nervous phenomena and ocular findings of exophthalmic goiter are caused by an abnormal thyroid agent. This led to the hypothesis that the clinico-physiologic complex of exophthalmic goiter varies with the total and relative amounts of the normal and abnormal thyroid agents. In 1914, Kendall obtained the active agent, thyroxin, 65 per cent of which by weight is iodin. This immediately led to speculation as to the possibility of an incompletely iodized thyroxin molecule being driven from the thyroid by intensive stimulation, and led me to the hypothesis that the clinico-physiologic complex of exophthalmic goiter is determined by the total and relative amounts of thyroxin and of an incompletely iodized thyroxin nucleus. This would have led much earlier to the therapeutic trial of iodin but for the fact that it seemed improbable that this could have been as thoroughly tried out as literature indicated without marked beneficial therapeutic effect having been generally recognized. While preparing an article for publication in Oxford Medicine,* I suddenly became convinced that there are many reasons why the action of iodin might have been misinterpreted. The chief of these was the lack on the part of observers of a correlation of the fluctuating findings throughout the course

*Functions of the normal and abnormal thyroid gland. Oxford Med., 1922, iii, 839-873.

of the disease on a clear-cut hypothesis of the presence of two factors, whether or not the factors are two products of the thyroid gland.

A partial interpretation of the findings and course of exophthalmic goiter in terms of a theory is at present, at least, essential for an understanding or at least for facility in grasping the results anticipated and obtained from the administration of iodin. The following facts are perhaps of outstanding significance:

1. Resection of the thyroid gland in many instances reduces the basal metabolism to normal and so far abolishes all other manifestations of the disease, at least for a period, that they are not detectable. In the majority of cases, the results, at least temporarily, approach abolition of the complex. This observation alone, almost invariably overlooked by the group of writers who have belittled the part played by the thyroid, is sufficient in the face of all conflicting evidence to warrant the tentative assumption that both the rise in basal metabolism and the characteristic phenomena of exophthalmic goiter are caused by products of the thyroid gland or of some abnormal thyroid function. Considering that only a portion of the gland is removed, failure in all cases to effect a complete remission and recurrences of the complex only strengthen the argument.

2. Almost any ratio of the degree of hyperthyroidism or of increase in basal metabolism to the characteristic nervous phenomena or ocular findings may be present in different cases or in the same cases at different periods in the course of the disease. Rather extreme cases may be used to illustrate. The basal metabolism may be normal when the nervous phenomena with or without associated ocular findings permit a diagnosis at a glance. In another case, or at another period in the same case, the basal metabolism may be +80 or higher and the nervous phenomena and the ocular findings character

istic of the physiologic status absent. Previous to the administration of iodin, I attributed the former complex to an excess of an abnormal thyroid agent and the latter to an excess of thyroxin, assuming the physiologic state to be the same as that in hyperfunctioning adenomatous thyroid. We now know that in the former complex all evidence of disease disappears in from seven to ten days following the administration of iodin and that the latter complex is not appreciably changed by such medication. The mildly hyperthyroid case with notable to marked nervous phenomena, and in some instances progressive exophthalmos, is most frequently seen following the resection of the thyroid, the remnant of which has not appreciably increased in size, and presumably at a time when a high degree of hyperthyroidism would otherwise be present. In this group, the stare and nervous phenomena disappear and the basal metabolism drops to within normal limits almost without exception within ten days. Progress in the degree of exophthalmos stops and frequently recession takes place. If, following resection of the thyroid, the remnant has enlarged, the basal metabolic rate is relatively high, the drop in metabolism will in general be proportional to the degree of the nervous phenomena. If nervous phenomena are absent, the basal rate will not as a rule drop. The same group of writers who have overlooked the effects of resection of the thyroid and belittled the part that the thyroid plays in exophthalmic goiter, have seized the mild postoperative complex to support some neurogenic theory and not infrequently to bolster up some therapeutic regime having but little influence on the course of the disease.

What are the factors which determine the relative and total amounts of thyroxin and the abnormal product delivered by the thyroid? They are intensity of thyroid stimulation, iodin supply, and training of the thyroid. That the first two are important factors is self-evident

and that the last might be a factor is almost equally evident. The hypothesis that periods of intensive stimulation alternating with periods of remissions, provided exacerbations and remissions happened to be favorably timed, will cause a physiologic as well as anatomic hypertrophy of the thyroid has, like most of the hypotheses presented in this paper, been daily checked against the findings and course of the disease in the analysis of cases under observation. I shall not discuss the hypothesis further than to state that a large thyroid relatively late in the disease is prone to deliver a large amount of thyroxin.

Although we have entertained and elaborated many etiologic theories, we are still in the dark when we go further back in the mechanism of exophthalmic goiter than the point indicated by the hypothesis that the thyroid is intensively activated by stimuli of unknown origin. The hypothesized mechanism of the thyroid in exophthalmic goiter is much as follows: A fluctuating degree of stimulation exists over a period of months or years. If the degree of stimulation is relatively low, thyroxin is delivered in sufficient quantities to cause hyperthyroidism without hypertrophy of the secreting cells. The degree of stimulation is as a rule sufficiently intense at the onset to cause hypertrophy and delivery of an abnormal product. The degree of stimulation required to cause hypertrophy is relatively high if an adequate supply of iodin is present in the thyroid. Stimulation is in many cases sufficiently high to cause hyperplasia of the alveolar epithelium and cell destruction. It is probable that very high degrees of stimulation cause a relatively high output of the abnormal agent and a relatively low total output. A well-trained gland with an adequate supply of iodin probably delivers more thyroxin under optimal stimulation than under higher degrees of stimulation. Hence, with regression of the

cause up to a certain point, the basal metabolism will rise with a regression of the phenomena attributable to an abnormal agent. Irrespective of the degree of stimulation, the thyroid will not elaborate much, if any, of the abnormal agent if plenty of iodin is available. If the abnormal agent is not being elaborated, increasing the iodin intake, as far as we have any definite evidence, has no effect on the thyroid output and hence none on the clinical complex. The relative and total amounts of thyroxin and the abnormal agent delivered by the thyroid are determined by an equation in which the degree of stimulation, available iodin, and training of the gland are important factors. There are undoubtedly unknown factors.

What is the nature of the hypothesized abnormal product? It is the intent here only to indicate the line of speculation that preceded the use of iodin. I wish to emphasize that if it does not prove to be a non-iodized molecule, the two-product hypothesis is not seriously invalidated. Thyroxin is a dynamic catalytic agent hastening the rate of energy transformation in the body. It is a remarkably stable agent and may continue to act for weeks before becoming exhausted. The evidence on which the idea of an incompletely formed thyroxin rests also suggests that its life is short, acting much as epinephrin; in fact, such an agent may be responsible for some of the findings that confuse efforts to correlate the function of the thyroid and the suprarenals. This agent may be responsible for the pigmentation present in many cases of goiter. It is also possible that some results of experimental stimulation of the thyroid and the introduction of various extracts of the thyroid intravenously are due to this agent. In his attempt to synthesize the thyroxin molecule, Kendall has obtained compounds, some of which may possibly be this agent.

Many reactions that might follow the administration of iodin were considered. The complete iodization of the thyroxin molecule in the tissues of the body seemed possible but not probable. That the iodin might lead to more complete iodization of thyroxin in the gland or that it might block its discharge seemed more probable. Many observations, beyond discussion here, suggested that an intensively stimulated thyroid is handicapped in its ability to pick up iodin from the circulation unless the concentration in the blood is high, and hence that large doses might tend partially to reverse the absorption and discharge mechanism of the gland. This led me to the trial of much larger doses of iodin than theory seemed to indicate and of Lugol's solution, since I thought that iodin might possibly be more available in this compound. I started the administration of iodin with the hope of correcting the physiologic status indicated by the nervous phenomena and ocular findings but did not consider a drop in the basal metabolism essential. The drop of basal metabolism in many cases to normal, following the administration of iodin, suggests that the abnormal agent is a catalyst acting similarly to thyroxin. It also suggests that when the production of the abnormal agent is stopped the delivery of thyroxin is diminished.

An attempt to answer these questions leads to much interesting speculation which cannot be considered here. Before Kendall obtained thyroxin, I attributed the elevated metabolism to a normal thyroid agent, presumably present in desiccated thyroid, and pointed out that another agent seemed to have a special affinity for the nervous system and that a third possibly caused the exophthalmos. I have never quite given up the concept of a third agent producing the ocular symptoms. For a long time, I have entertained the hypothesis, and built up evidence to support it, that

the abnormal product made the central nervous system (when at relative rest) irritable and sent out stimuli which maintained the metabolism level above that maintained by an excess of the normal agent, and that this specifically irritable nervous system was very sensitive to psychic influence which still further elevated the metabolic rate in many cases.

I began the administration of Lugol's solution in ten minim doses once, twice or three times a day in March, 1922, starting after the patient had been in bed for a period, that I might better distinguish the action of iodin from the results of rest. At first I selected more or less definite types. The iodin was continued up to the day of operation and then stopped. By the end of the year the program followed at present was adopted. For the first ten days of treatment 10 minims of Lugol's solution is given three times a day. For patients operated on, this dosage is continued up to operation and throughout the postoperative reaction, even though the operation is postponed for several weeks. In cases that have not been controlled by operation and "recurrent" cases and all cases in which operation has been indefinitely postponed, the dose is reduced to 10 minims daily in from ten to fourteen days.* Following the postoperative reaction, 10 minims daily are at the present time given as a routine for eight weeks. If following this there is a recurrence, iodin is given for three months if it completely controls, and is then discontinued. This program is followed out as long as "recurrences" occur and are completely controlled by iodin. If they are not controlled, a second resection of the thyroid is performed. When immediate control is necessary, as in crisis, I aim to give from 50 to 100 minims in divided doses by mouth or rectum within one

*In the hospital the drug is measured in minims; outside, the patients measure it in drops.

or two hours after the patient comes under observation. The first year sodium iodid was given intravenously to a few patients. I have come to rely almost wholly on oral administration even when constant vomiting is present. Definite results from the administration of iodin may be noted within two hours or less. The maximal result is, as a rule, obtained on the sixth or seventh day. On one of these days, basal metabolism is likely to fall precipitously. When the administration of iodin is stopped, the complex may completely return in three or four days. It is probable that at least a partial loss of control occurs much sooner than this. Complete control is in many cases lost in ten days. The vomiting of crisis is invariably stopped within forty-eight hours. Not rarely a patient who has been in crisis for days or weeks will take food without vomiting the day that Lugol's solution is started. Patients in coma are rational within a few hours.

Our most accurate knowledge of dosage is obtained from a group of patients returning after thyroidectomy with a basal metabolism from 20 to 40 per cent above the average normal and a mild to frank complex of nervous phenomena, stare, and in some instances rapidly progressing exophthalmos; between the seventh and tenth days of the administration of 10 minims of Lugol's solution, the basal metabolism drops to normal and all manifestations of the disease disappear except the exophthalmos which, if previously progressive, diminishes in degree. The results in many cases have been spectacular. A normally athletic traveling salesman thrashing about in bed, "a wreck," there because of auricular fibrillation and myasthenia, was on the tenth day after starting 10 minims of Lugol's solution in apparent good health, exercising on the horizontal bars in a gymnasium. The basal metabolism had dropped from +23 to –7. For nine years he had been half invalid, never free from

the manifestations of exophthalmic goiter, although partially relieved by thyroidectomy years before (1916). On the tenth day, the dosage of Lugol's solution was changed to 5 minims daily. Ten days later he returned in his former condition with nervous phenomena, and so forth, and basal metabolism +23. He was again placed on 10 minims of Lugol's solution, told to go "on the road" and do as much as his strength permitted. Ten days later, he returned in good health, the basal metabolism being –7.

This and many other cases in which I have been able to carry out a definite control by repeated administration and withholding of iodin demonstrate that from 5 to 7 minims may have absolutely no effect when from 8 to 10 minims give absolute control. (This is in accord with much evidence suggesting that the thyroid gland cannot readily, at least, both discharge its product and absorb thyroxin at the same time.) I have quite definite evidence that 20 minims daily are required in some cases and less evidence that from 30 to 40 minims may at times give better control than 20 minims in severe cases. Some cases have been controlled continuously for more than two years except for short periods during which the administration of iodin was stopped to determine the necessity of continuing it. Disagreeable dermal and gastric disturbances have seldom been annoying. In one case swelling of the parotid gland occurred, abated and did not recur when the administration of iodin was resumed. We do not know the relative effective units of Lugol's solution and iodin in other combinations.

The results obtained can be stated by enumerating those that the hypotheses indicate should be obtained if iodin stopped or impeded the delivery of an abnormal agent: (1) the disappearance of the "stare"; (2) the disappearance of the characteristic nervous phenom-

ena, including the crisis, and the avoidance of crisis death; (3) cessation in the development of exophthalmos and in some cases rapid regression; (4) reduction of the entire physiologic status to that of hyperfunctioning adenomatous goiter; (5) reduction of the syndrome to that of hyperfunctioning adenomatous goiter except for the anatomic findings in the thyroid, the exophthalmos, and minor physical findings which may remain, an index of a preëxisting status, unless the patient is too near a moribund state before the iodin is started; (6) marked reduction of the nonoperative mortality; (7) reduction of operative mortality to a percentage approximately that of hyperfunctioning adenomatous goiter; (8) the reduction of the operative mortality to approximately that of the group of cases coming from that portion of the United States east of a line drawn north and south through the State of Indiana, before iodin was used, and (9) absolute abolition of the mortality both nonoperative and operative so far as it is attributable to the crisis status and the infectious processes originating in the crisis, provided the iodin is administered sufficiently early in the disease.

Is the control of that part of the complex attributed to an abnormal product absolute? In other words, will the administration of Lugol's solution in cases of exophthalmic goiter in amounts somewhere between 10 and 40 minims daily from the inception of the disease ever be followed by the characteristic complex even though hyperthyroidism becomes intense? That the evidence warrants seriously considering an affirmative answer is significant.

After complete control of the characteristic complex and a drop in basal metabolism, the latter with all its attendant phenomena in some instances rises to a height far above that existing previous to the administration of Lugol's solution. Does this indicate that the beneficial

results from the administration of iodin are of short duration as many critics have indicated? If a negative answer is given, is the elevation of basal metabolism higher than it would have been if iodin were not given? Alternation of exacerbations and remissions in the course of the phenomena attributed to the abnormal product is an outstanding characteristic of the disease. A curve representing these fluctuations and another those of the basal metabolism in the average case run more or less parallel but often diverge. Not rarely, one may be high when the other approaches the base line. On the two-product theory, the heights of the curves are determined by intensity of stimulation, free iodin supply, training and fatigue of the thyroid, as well as unknown factors. All these factors may have almost any relationships in time and degree. Tendency to parallelism in the two curves is determined largely by intensity of stimulation, and divergence by the other factors. To avoid faulty interpretation, one must conceive that the intensity of the nervous phenomena is determined by the reaction of the nervous system to the abnormal product as well as by the amount of that product, and hence can only within certain limits be used to judge the degree of intoxication. Many times crisis and death have confronted me a few hours after expressing an opinion that the patient was relatively safe.

Out of a series of cases can be selected many with a course approximating the following: general increase in intensity of all phenomena into the last quarter of the first year; near crisis or crisis status; basal metabolism from +40 to +60; sudden or gradual remission followed by a rapid rise in metabolic rate to +70 or +80 without recurrence of nervous phenomena or stare. In the latter condition, the patient may be phlegmatic and obese. This picture either with high or relatively low basal metabolism is the one that sur-

geons have striven for in preoperative management. The extreme fluctuation from a crisis with relatively low basal metabolism to a complex of high intensity attributable to thyroxin was the framework on which the two-product theory was built. It was this change in the course of the disease that I hoped to cause by the administration of iodin. It seemed quite possible that under intensive stimulation and a relatively deficient supply of iodin a functional status in the gland obtained in which it could not fully utilize the iodin available in the blood stream. In the average case, the phenomena attributable to the abnormal product, although fluctuating in degree, are present throughout the greater part of the disease. I did not anticipate control of the complex caused by an excess of thyroxin and now have no evidence on which to assume that elevation in basal metabolism following control of the complex attributable to the abnormal product is caused by the iodin administered, or that the effects of iodin are temporary. No drop in basal metabolism is obtained in those cases with high basal metabolic rates and in which the clinical picture, in conjunction with a history of the course of the disease, makes me confident that the complex present is entirely attributable to an excess of thyroxin in the body. There is some evidence that iodin temporarily to a degree checks the delivery of thyroxin.

In attempting to correlate the clinical complex of exophthalmic goiter with the two-product hypothesis one should bear in mind the following categorical statements: (1) the nervous phenomena when intense may not be pathognomonic; on the other hand, when mild they may be pathognomonic; (2) intoxication from the abnormal product may be of a high degree with relatively mild nervous phenomena; (3) marked nervous phenomena may be atypical; (4) exophthalmic goiter frequently develops in patients of a neurotic type, or with frank

neurasthenia, which frequently becomes more manifest when the mind during remissions is less occupied with the more serious complaint; (5) the interpretation of ocular findings is full of pitfalls; this is particularly true of the stare which may be present irrespective of the presence of exophthalmos, which, when not progressive, is not an index of the existing physiologic status; (6) the hyperthyroidism of adenomatous goiter may to a degree simulate that of exophthalmic goiter, and (7) there is a large group of persons, many of whom are of an asthenic type, whose basal metabolism ranges from the average normal to 25 per cent below. The members of this group may develop, perhaps are more prone to develop, exophthalmic goiter than the average person. The reason for the low basal metabolism in this group is unknown.

The most valuable test, not barring estimations of basal metabolic rate, at command in the diagnosis of mild cases is the effect of iodin on the nervous phenomena. Checking with estimations of the basal rate of course adds enormously to the value of the test. This requires accurate determinations of basal rate for a time before and after the period of from seven to fourteen days during which Lugol's solution is administered. It must be borne in mind that a neurotic patient having exophthalmic goiter when the thyroid is delivering an excess of thyroxin only will not be affected by the administration of iodin, and there is a chance of starting the iodin when the basal metabolic rate is rising.

The use of iodin in the clinic decreased the surgical mortality from approximately 3.5 per cent to approximately 1 per cent in cases in which operation was performed in Rochester. From two to four postoperative deaths, the number depending on interpretation, have occurred with intense postoperative reactions similar

to the typical crisis of exophthalmic goiter. I am of the opinion that these "hyperthyroid reactions" were the same as those occurring in hyperfunctioning adenomatous goiter and not those typical of exophthalmic goiter.

Ligation of the thyroid arteries with all the attendant suffering, morbidity and expense has been almost abandoned.

The preoperative deaths have been reduced from twenty-five to thirty to from two to five for each 1,000. The latter deaths have all been due to complications such as pneumonia, phlebitis, septic emboli and lung abscess.

Perhaps the most satisfactory result of iodin therapy to both patient and physician has been the control of the recurrent or continued manifestation of the disease. In many cases, this means the complete elimination of nervous phenomena, frequently disabling, that could not previously be definitely attributed to the thyroid. These complaints were often looked on by the surgeon as evidence of damage by the preëxisting hyperthyroid state and were often cited by many observers to belittle the part played by the thyroid in the complex of exophthalmic goiter.

Mild postoperative cases perhaps offer the most convincing support of the two-product theory. Following this theory, sufficiently extensive resection of the thyroid should result in an intensively stimulated remnant of thyroid delivering a subnormal amount of thyroxin and some of the abnormal agent. In accord with this is the observation that in mild recurrent cases, the nervous phenomena and not infrequently progressive exophthalmos are the outstanding features, although the basal metabolism is relatively low.

One patient, at present under observation, had, before thyroidectomy, a basal metabolic rate ranging above +80, and since operation a rate of –14, characteristic

nervous phenomena, and progressive exophthalmos. When this patient is placed on Lugol's solution, the nervous phenomena disappear, exophthalmos recedes, basal metabolism drops to –28, and edema, slow speech, and so forth, the characteristics of myxedema, appear within two weeks. When iodin is administered and the basal metabolism is maintained at the average normal with thyroxin, there is no evidence of disease except slight exophthalmos. Many similar cases have been observed although this is the only one in which the basal metabolism has dropped low enough to have myxedema apparent and unquestionable on inspection. Without going into detail, I will state that I have seen the complex that terminates in a panophthalmitis and loss of the eyes progress rapidly almost to the point of forcing enucleation, stop and begin to recede within five hours after 100 minims of Lugol's solution had been given.

The two-product theory indicates that if sufficient and, when necessary, repeated resection of the thyroid and administration of iodin are followed up, complete control of the disease can be maintained until the cause disappears. It is too early to express a definite opinion, although the evidence indicates that the patient with exophthalmic goiter on a program of resection and administration of iodin need not be disabled much longer than the time devoted to the operations. In the majority of cases but one resection of the thyroid is required. This program can be carried out with less risk, suffering, morbidity and expense than any other method of treatment so far proposed, even though we grant far more efficacy to roentgen rays, "medical management," and so forth, than has even been demonstrated or even claimed by the majority of advocates of these methods.

It should be borne in mind that the present operative mortality of 1 per cent in the Mayo Clinic is not the

mortality attending this program. The mortality is confined largely to a group of cases, a large percentage of which occur because this program is not followed before they are under observation. Iodin is the only tool in the hands of the internist that gives sufficiently clear-cut results to permit of definite interpretation. How far the trial of iodin administration, avoidance of stresses, and other symptomatic medication under critical control should be pursued early in the history of the disease before resorting to surgical measures, is an open question.

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